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THE INCIDENCE OF INTESTINAL PARASITES IN DURBAN FACTORY WORKERS

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In a previous paper[1] we compared the incidence of parasites in two different areas of Durban, one of which, Cato Manor, is a notorious slum, and the other, Chesterville, is a sub-economic housing scheme. In this paper we showed that there was no significant difference in the incidence of protozoal parasites as between Cato Manor and Chesterville but, on the other hand, better housing conditions were associated with a lower incidence of helminths.

This paper records the result of a parallel test in African factory workers, the majority of whom are housed in barracks and all of whom received at least one meal a day provided by the factory at a nominal charge. A single stool specimen from each case was examined directly and by zinc-sulphate flotation. Where the identity of a parasite was in question, staining or other appropriate investigation was done.

Table I shows the results together with corresponding figures for Cato Manor and for Chesterville. The figure P shown against these two latter indicates the probability that any difference observed might have occurred by chance.

The incidence of *Trichocephalus* in the factory is not signi-

TABLE I. INTESTINAL PARASITES: SURVEY IN A DURBAN FACTORY

	This Survey		*Cato Manor*		*Chesterville*	
	No.	*%*	*%*	*P*	*%*	*P*
Trichocephalus trichiura	286	43·5	60·3	<·01	39·5	·17
Strongyloides stercoralis	—	—	1·0	—	0·2	—
Heterodera spp.	4	0·6	2·0	·05	2·1	·03
Hookworm *spp.*	44	6·7	5·7	·50	4·5	·09
Oxyuris vermicularis	—	—	0·6	—	0·2	—
Ascaris lumbricoides	244	37·1	50·3	<·01	26·1	<·01
Schistosoma spp.	6	0·9	1·8	·19	0·4	·32
Hymenolepis spp.	2	0·3	0·6	·45	0·4	·80
Taenia spp.	73	11·1	11·0	·95	5·3	<·01
Entamoeba histolytica	52	7·9	17·4	<·01	15·2	<·01
Entamoeba coli	265	40·3	55·0	<·01	52·7	<·01
Endolimax nana	111	16·9	27·8	<·01	26·7	<·01
Iodamoeba butschlii	34	5·2	12·1	<·01	9·7	<·01
Chilomastix mesnili	4	0·6	3·7	·73	2·5	<·01
Giardia lamblia	21	3·2	3·7	·65	4·9	·16
Monads	3	0·5	1·8	·05	0·6	·80
Coccidia	1	0·2	1·0	·11	0·6	·32
All metazoa	428	65·0	78·5	<·01	56·2	<·01
All protozoa	320	48·6	68·3	<·01	67·5	<·01
All parasites	547	83·2	92·6	<·01	82·3	·62

The figure *P* gives the probability that the observed difference may be due to chance. Where this figure is less than ·01 the difference may be considered as significant.

ficantly different from that in Chesterville, but is considerably lower than that in Cato Manor. The Hookworm *spp.* have approximately the same incidence in all three groups as have also the Schistosomes. For *Ascaris*, the factory, while better than Cato Manor, is considerably and significantly worse than Chesterville. For *Taenia spp.* with a different epidemiology, the incidence in the factory and in Cato Manor are much the same, and are both much higher than is found in Chesterville. In the over-all incidence of metazoa the factory is better than Cato Manor but significantly worse than Chesterville.

Study of the protozoa shows a different picture. The incidence of *Entamoeba histolytica* in the factory is less than half of that in Cato Manor and about 45% of that in Chesterville. A similar difference holds for all the protozoa occurring in any large numbers except for *Giardia lamblia*. The incidence of the protozoa over-all is only 70% of that in either of the two previous surveys.

Thus, though the factory shows a higher incidence of parasites than Chesterville, this is made up by an increase in the metazoa, which is partially balanced by a marked decrease in the protozoa. Table II shows the weight of infestation. It will be seen from this table and from the

TABLE II. WEIGHT OF INFESTATION

Parasitic species per patient	*This Survey* %	*Cato Manor* %	*Chesterville* %
0	16·9	7·4	17·7
1	40·4	17·8	23·9
2	21·4	27·8	26·1
3	16·0	20·9	18·1
4	3·6	14·9	10·7
5	0·8	7·8	2·9
6	0·3	2·0	0·6
7	—	1·2	—
8	0·2	0·2	—

histogram (Fig. 1) that a higher proportion of the factory workers have fewer parasites and, though multiple infestation occurs occasionally, it is by comparison a rarity. In fact, 80% of the subjects had one helminth species or less and

TABLE III. SPECIES PER PATIENT

	This Survey %	*Cato Manor* %	*Chesterville* %
Protozoa	0·64	1·23	1·12
Metazoa	0·88	1·33	0·79
Parasites	1·53	2·56	1·91

87% had one protozoon species or less. Table III gives the average number of parasitic species per patient and here we see further evidence of the relatively low incidence of protozoa.

These results are difficult to explain. It is true that the examinations were carried out at different times, but it is unlikely that there should be such a great variation for the period in question. Just why do the factory workers have more worms and fewer protozoa than the population living in the village? Generally speaking, and as is evidenced by our previous work in the comparison of Cato Manor and Chesterville the helminth population drops under conditions of good hygiene. This follows from the fact that most of the worms have to pass some period of their existence outside the human body and reinfection is necessary to maintain the

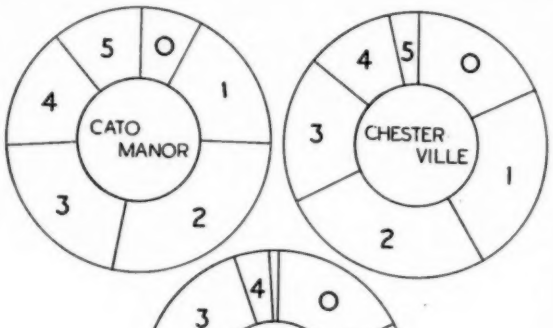

Fig. 1. Durban factory: parasite species per patient.

helminth load. Unless such reinfection is occurring outside of the factory, the figures cannot be explained.

Reinfection is not necessary for the protozoa and, in fact, other things being equal, once a protozoon has established itself in a host it will remain there and reproduce itself in the host. This is evidenced by the relatively small change in protozoa as between Cato Manor and Chesterville. There must, however, be something in the factory worker's life which is inimical to protozoa, but which does not affect the incidence of the helminth. The only factor which is apparent is the availability of a good meal.

SUMMARY

A survey has been carried out on a group of factory workers in Durban and the figures compared with those from previous surveys on Cato Manor—a slum—and Chesterville—a sub-economic housing scheme. The incidence of the protozoa is markedly lower than either of the other two surveys, whereas that of the helminths is lower than that of the slum, but higher than that of the housing scheme.

Our thanks are due to the staff of the factory for their cooperation in this work.

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VAN DIE REDAKSIE

TOLBUTAMIED BY DIABETES EN VERWANTE AANGELEENTHEDE

Dit blyk dat tolbutamied (D 860; handelsname Orinase, Artosin, Rastinon) 'n vaste plek in die behandeling verower het. Dusver het daar nog geen kragtiger stowwe, wat terselfdertyd so weining toksies is, hul verskyning gemaak nie.* Die ouer mondelikse hipoglisemiese middel, karbutamied, is heelwat op die agtergrond geskuif omdat dit meer geneig is (as tolbutamied) om ligte newe-effekte en, nou en dan, ernstige leukopenie te veroorsaak. Daar kan egter nie aan getwyfel word dat dit 'n ietwat kragtiger middel is wat die verlaag van bloedsuiker betref nie, en daar is heeltemal genoeg regverdiging vir sy gebruik by geleentheid by pasiënte wat nie op tolbutamied reageer nie, mits die wit bloedseltelling noukeurig dopgehou word en mits die simptoom van 'n seer keel as noodgeval beskou word. Ons verdoem tog per slot van rekening nie die tiourasiele omdat hulle hier en daar 'n soortgelyke ongeluk veroorsaak nie. Dit is interessant dat Duitsland nog geen verslae van agranulositose op karbutamied opgelewer het nie, hoewel daar 8 gevalle in die Verenigde State gerapporteer is. Dit is in werklikheid twyfelagtig of karbutamied werklik vir die meeste van hierdie sterfgevalle verantwoordelik was—dit kon blote toeval gewees het. Een geval van ernstige totale agranulositose is in Suid-Afrika aangemeld;[2] die pasiënt het herstel.

Hierdie week doen beide die Johannesburgse[3] en die Kaapstadse[4] werkers verslag oor hul verdere ondervinding met tolbutamied. Eersgenoemde groep herinner ons aan die feit dat ons glad nie weet of ons die intree van latere bloedvatkomplikasies vertraag of versnel nie, alhoewel ons hierdie stof ewe goedsmoeds gebruik om abnormaal hoë bloedsuikergehaltes te verlaag. Ons weet nog nie hoe tolbutamied te werk gaan nie, maar ons weet wel dat dit *nie* soos insulien ageer nie en dat dit minder uitwerking, indien enige, op die periferale opgebruik van glukose uitoefen. Dit kan m.a.w. gesê word dat tolbutamied nie die grondslagtelike versteuring in die stofwisseling verander nie, maar die bloedsuikergehalte op 'n ander wyse (waarskynlik deur 'n lewermeganisme) verlaag. Natuurlik kan ons ook redeneer dat selfs insulien nie by die algemeenste, ouer soort suikersiektelyer die onderliggende afwyking raak nie, aangesien daar by hierdie soort diabetes nie juis aanvanklik 'n tekort aan insulien bestaan nie. Tolbutamied mag dus nie verdoem word omdat dit anders as insulien is nie—en in elk geval weet ons almal dat daar talle gevalle voorkom waar insulien hoegenaamd nie die ontwikkeling van bloedvatletsels voorkom nie. Tolbutamied verminder nie die serum-cholesterol by diabetiese pasiënte nie, en hierdie feit kan, op sy minste,

EDITORIAL

TOLBUTAMIDE IN DIABETES, AND SOME RELATED CONSIDERATIONS

It seems as though tolbutamide (D 860; trade names Orinase, Artosin, Rastinon) is here to stay. No more potent substances which are also as little toxic have yet appeared over the horizon.* The earlier oral hypoglycaemic agent, carbutamide, has largely been superseded because of its greater tendency to produce mild side-effects and occasional severe leucopenia. There is little doubt, however, that it was a somewhat more potent blood-sugar-lowering agent, and a fair case could be made out for its occasional use in patients who were not responding to tolbutamide, provided that a careful check was kept on the white-cell count and that the symptom of sore throat was treated as an emergency. After all, we do not condemn the thio-uracils because of a rare accident of similar nature. It is interesting that no fatal cases of agranulocytosis on carbutamide have been reported from Germany, although 8 have been collected from the United States.[1] Actually it is very doubtful whether carbutamide was responsible for most of these deaths—whether they were not coincidental. In South Africa one case of severe total agranulocytosis has been reported;[2] the patient recovered.

This week the Johannesburg[3] and Cape Town[4] workers both report on their further experiences with tolbutamide. The latter group remind us that, although we may blithely reduce abnormally high blood sugars with it, yet we have no idea whether we are preventing or hastening the onset of later vascular complications. We do not yet know the mode of action of tolbutamide, but we do know that it does not act in the way that insulin does, and that it has less, if any, effect on the peripheral utilization of glucose. In other words it may be said to leave the underlying metabolic disorder unchanged, reducing the blood sugar by a different and probably hepatic, mechanism. Of course we can also argue that in the commoner, older type of diabetic patient even the use of insulin is not getting at the basic disorder, since there is no real deficiency of insulin to start with in this type of diabetes. We cannot therefore condemn tolbutamide because it is not like insulin—and anyway we all know that in many cases insulin by no means prevents the

* A new substance DBI has been introduced in America, which is said to be more powerful and will, we believe, be shortly undergoing a clinical trial in South Africa.

* 'n Nuwe stof, DBI, is so pas in Amerika gebruik en is na bewering nog kragtiger, en ons verstaan dat dit binnekort 'n kliniese toetsgebruik in Suid-Afrika sal ondergaan.

beskou word as 'n wenk dat dit nie die oormatige graad kroonslagaarvervetting wat met diabetes gepaard gaan (veral by vroue), sal verminder nie.

In hulle toetse van tolbutamied by pasiënte op insulien, het die Kaapstadse dokters die probleem op 'n oorspronklike maar interessante wyse benader. Hulle het probeer om alle insulien vir 'n paar weke lank af te skaf voordat hulle die tablette begin gebruik het, en hulle is beloon met die ontdekking dat daar baie pasiënte was wat eintlik geeneen van die twee stowwe nodig gehad het nie! Hierdie metode het dan ook tot 'n mate die voordeel dat dit elke pasiënt sy eie kontrole maak. Dit is waarskynlik die beste metode om te gebruik in die diabeteskliniek, waar ervare klinici aan die hoof staan, maar dit kan nouliks aanbeveel word in die algemene praktyk want, soos Jackson[4] skryf, is dit ‚nie altyd maklik om te weet by watter suikersiektelyers insulien sonder gevaar afgeskaf kan word nie'. Dit is egter altyd 'n verstandige reël dat die pasiënt haar insulien of haar tolbutamied moet verdien het. Met ander woorde: By die ligte geval van 'n nie-kototiese pasiënt oor die 40 jaar moet koolhidraatbeperking steeds die eerste staatmaker in die behandeling bly, en die dokter moet nie sy toevlug neem tot insulien of mondelikse middels voordat dieetbehandeling alleen, en deeglik, op die proef gestel is nie. Dit is heel moontlik dat baie pasiënte in algemene praktyke en klinieke onnodig insulien gebruik, en 'n kort oorsig van sy waarde by elke afsonderlike geval sal moontlik baie interessant, heilsaam en selfs 'n bietjie aanmoedigend wees. Jackson[4] maak daarop aanspraak dat hy al pasiënte teëgekom het wat beter beheer kon word sonder enige middels dan terwyl hulle insulien gebruik het.

Hierdie feite bring ons dan tot 'n bespreking van die soort pasiënt wat baat sal vind by tolbutamied. Dit kan nie weerlê word dat dit nie gebruik mag word (behalwe as proefneming) by enige pasiënt met die ernstige, jong soort suikersiekte nie, of wat ooit onderhewig was aan diabetiese ketose nie. Daar bestaan min rede om tolbutamied en insulien tesame te gebruik, en glad geen regverdiging vir so 'n gesamentlike gebruik in die algemene praktyk nie. Schneider en sy medewerkers[3] haal Dunlop se ander maatstawwe[5] vir die probeer van die mondelikse middels aan, nl. die pasiënt moet nie meer as 40 eenhede insulien daagliks benodig nie, en die vastende bloedsuikergehalte wanneer die pasiënt *nie* insulien gebruik nie moet minder as 300 mg. per 100 ml. wees. Vir hospitaalgebruik is geeneen van hierdie twee maatstawwe streng korrek nie. Die hoeveelheid insulien wat 'n pasiënt nodig het om die bloedsuiker te beheer is geen maatstaf van die erns van sy diabetes nie, as dit bereken moet word volgens onderhewigheid aan ketose nie. Sommige ouer pasiënte kan inderdaad onbeheer wees op 200 eenhede daagliks en byna of geheel en al onveranderd bly op glad geen insulien nie, terwyl 15 eenhede daagliks by 'n jong lyer die hele verskil tussen lewe en dood kan maak. Tog gebeur dit soms dat 'n ouer persoon die ernstige ‚jong' soort diabetes ontwikkel, en die saak kan dus nie somaar afgehandel word met die bewering dat tolbutamied sonder gevaar by alle pasiënte oor die 40 jaar gebruik kan word nie. Dit is gewis veilig om dit by enige pas ontdekte suikersiektelyer te gebruik, of by enige lyer wat nie insulien neem nie en ook nie ketoties is nie en wat verkieslik nie die ernstige simptome van diabetes (vinnige gewigafname, kwaai poliurie en swakheid) toon nie. Maar by ten minste die ligte geval is die dieet hoofsaak. Terloops,

development of vascular lesions. Tolbutamide does not lower the serum cholesterol in diabetics and this may be taken as a suggestion, at least, that it will not diminish the excessive degree of coronary atheroma which is associated with diabetes, especially in the female.

In their trial of tolbutamide in patients who were taking insulin, the Cape Town workers tackled the problem in an unusual but interesting manner. They attempted to stop all insulin for a few weeks before using the tablets, and were rewarded by finding many patients who did not really need either! This method also has the advantage, to some extent, of making each patient his own control. It is probably the best method to use in the diabetic clinic, where experienced clinicians are in charge, but could hardly be recommended in ordinary general practice, for, as Jackson[4] remarks, 'it is not always easy to know in which diabetics it is safe to stop insulin'. It is, however, a good rule that a patient should have earned her insulin or her tolbutamide. In other words, in the mild, over-40, non-ketotic patient, carbohydrate restriction must still be the first stand-by in treatment, and insulin or oral drugs should not be resorted to until diet has been tried alone, and tried properly. Quite probably many patients in practices and clinics are taking insulin unnecessarily, and a short review of its value in each case might prove interesting, salutary and even somewhat heartening. Jackson[4] actually claims to have found some patients who were better controlled off all drugs than they were while taking insulin.

This leads us to consider the type of patient for whom tolbutamide is suitable. There can be no doubt that, except experimentally, it should not be used in any patient who has the severe, young type of diabetes, or has ever been in diabetic ketosis. There is little indication for using tolbutamide and insulin together, and none at all in general practice. Schneider and his co-workers[3] quote Dunlop's other criteria[5] for trial of the oral drugs, which are that the daily insulin requirement should not exceed 40 units, and the fasting blood sugar when not on insulin should not exceed 300 mg. per 100 ml. Neither of these criteria is strictly correct for hospital practice. The amount of insulin needed by any patient to control the blood sugar is no indication of the severity of the diabetes, if this is to be judged by a liability to ketosis. In fact some older patients may be uncontrolled with 200 units of insulin daily, yet are little or no different with none at all, whereas 15 units a day in a young diabetic may make all the difference between life and death. Sometimes, however, an older person may develop the severe 'young' type of diabetes, so that the matter cannot simply be resolved by saying that tolbutamide may be safely used in all patients over 40. It is certainly safe to use it in any newly discovered diabetic, or in any diabetic not taking insulin, who is also not in ketosis, and preferably who does not show the severe diabetic symptoms of rapid loss of

beide die Kaapstadse en die Johannesburgse groepe was bly om te merk dat behandeling met tolbutamied 'n gunstige reaksie uitgelok het by verskeie te maer lyers aan ligte diabetes; hulle kon meer eet en het vetter geword, terwyl hul glikosurie afgeneem het.

Oor die algemeen stem die twee groepe werkers saam oor al die belangrike punte. 'n Teleurstelling wat albei groepe ondervind het was die verslegting in die siektebeheer wat by verskeie pasiënte voorgekom het na enige maande van tolbutamiedbehandeling. Schneider *et al.*[3] meen dat dit te wyte is aan die feit dat die pasiënte minder noukeurig op hul dieet begin let het, en het opgemerk dat die pasiënte almal vetter geword het. Dit kan ook wees dat die eintlike uitwerking van die middel ook geneig is om te vervaag. In elk geval is dit belangrik om op die hoede te wees vir enige tekens dat die beheer van die siekte verswak.

Hoewel tolbutamied 'n groot stap vorentoe is in die behandeling van suikersiekte, kan die ware belangrikheid daarvan nog nie bereken word nie, en dit kan gewis nie die waarde van insulien oortref nie. Eintlik is dit amper méér 'n geleentheidsmiddel dan 'n onontbeerlike middel. Ons moet verwag dat dit die voorloper sal wees van ander, kragtiger mondelikse diabetesbestryders, maar dusver is daar nog geen ander middels van dié soort wat algemeen gebruik kan word nie. Geneeshere moet gewis wegbly van die ander mondelikse preparate wat in hierdie land deur verskillende fabrikante aangebied word.

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2. Jackson, W. P. U. en Herman, J. B. (1956): S. Afr. T. Geneesk., **30**, 904.
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4. Jackson, W. P. U. (1958): *Ibid.*, **32**, 000.
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weight, gross polyuria and weakness. But in the mild case at least, diet comes first. Incidentally both the Cape Town and Johannesburg groups were pleased to note good response to tolbutamide therapy in several over-thin mild diabetics who were enabled to eat more food and gain weight, while their glycosuria declined.

In general, the two groups of workers agree on all important points. One disappointment noted by both was the deterioration in diabetic control which occurred in a number of patients after some months on tolbutamide. Schneider *et al.*[3] think that this occurs because the subjects become lax about their diet, and they noticed that they all gained weight. It may be that the actual effect of the drug tends to wear off also. In any event it is important to watch for any worsening of control.

Although tolbutamide is an advance in diabetic therapy its true importance cannot yet be assessed, and certainly it cannot rival insulin in value. It is almost more a drug of convenience than of necessity. We must expect it to be the forerunner of other and more powerful oral anti-diabetic agents, but as yet there are none which can be generally used. Certainly the other oral preparations offered by various people in this country should be strictly left alone.

1. Kirtley, W.F. (1957):Diabetes, **6**, 72.
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FURTHER EXPERIENCES IN THE USE OF TOLBUTAMIDE (D 860) IN DIABETES MELLITUS

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Since 1955 a great deal of interest has been stimulated in the treatment of diabetes mellitus by the introduction of oral substitutes for insulin.[1-3] The original substance used was N-sulphanilyl-N′-butyl-carbamide, also known as carbutamide, BZ 55, or Nadisan. It soon became evident that, although certain diabetics could be controlled with carbutamide, toxic effects constituted a hazard. Kirtley[1] reported on 8 deaths in 7,193 cases treated. These toxic effects consisted of generalized sulphonamide sensitivity, agranulocytosis, thrombocytopenia, and hepatic and myocardial changes. The use of carbutamide has therefore been discontinued and it has been superseded by a new substance N-(4-methyl-benzenesulphonyl)-N′-butyl-urea, known as tolbutamide, D 860, Rastinon, Orinase or Artosin.

Tolbutamide has been the subject of clinical trials by many workers in different countries, and it is estimated that 150,000 patients have been treated. The hypoglycaemic effect is similar to that of carbutamide but the toxic effects are minimal. Allergic skin rashes, gastro-intestinal symptoms, leucopenia and thrombocytopenia[5, 6] have been reported, but these have not been severe. The results of numerous clinical trials have revealed that tolbutamide is successful in controlling the hyperglycaemia of a highly selected group of diabetic patients. Dunlop[7] has described as follows the type of diabetic most likely to respond:

1. They should have developed the disorder over the age of 40 years.

2. They should have shown no previous tendency to develop ketosis easily.

3. Their daily insulin requirements should not exceed 40 units.

4. Their fasting blood glucose when receiving no insulin should not exceed 300 mg. per 100 ml.

Not all patients conforming to these criteria respond to

tolbutamide and the most recent British results show adequate control in only 52% of these cases.[8]

Although these substances have been used for about 2 years, their exact mechanism of action has not been elucidated. It has been shown that they are effective only if some insulin is being produced by the patient and that they usually fail in the insulin-deficient patient.[9] They do not simulate insulin by increasing peripheral utilization of glucose.[10] As they have no effect on the depancreatized subject it has been suggested that they act by stimulating the production of insulin by the B-cells of the islets of Langerhans.[11] Other workers[12] have shown that they prevent the output of glucose from the liver by interfering with enzyme systems.

A most important aspect, which will be answered only after several years of observation, is the effect of tolbutamide in preventing, postponing or controlling the late manifestations of diabetes. At the moment we know that it lowers the blood sugar in certain patients, but we are ignorant of its effect on other metabolic processes in the diabetic. Elucidation of this problem will determine whether tolbutamide has a place in the long-term treatment of diabetes.

Two of the present authors reported on their early experiences with carbutamide and tolbutamide in a previous publication.[13] The object of this paper is to report further on our experiences with tolbutamide.

SUBJECTS AND METHODS

105 patients attending the Diabetic Clinic of the Johannesburg General Hospital were selected for tolbutamide therapy. The consisted of 17 males and 88 females between the age of 43 and 84 years. The duration of diabetes varied from 2 months to 30 years, and the age of onset from 36 to 75 years.

During the course of the investigation these patients have attended the clinic regularly for periods of up to 1 year. They were seen at frequent intervals by at least one of the authors and were instructed to test their urines for sugar with Benedict's solution 4 times daily (before each meal and at bedtime). They were told to report immediately if any untoward symptoms occurred (sore throat, rash or temperature) or if urine tests were unsatisfactory. All side-effects were carefully observed whenever they appeared.

The dosage of tolbutamide did not exceed 3 g. daily. A dose of 3 g. was employed on the first day, and this was decreased by 0·5 g. per day until a maintenance dose of 1·0 - 1·5 g. daily was reached. Initially the total daily dose was given before breakfast each morning but, as several patients experienced hypoglycaemic symptoms of giddiness and headache during the morning, the plan adopted was to administer the drug in 3 equal doses either before or after meals.

Where the previous dose of insulin did not exceed 20 units, insulin was discontinued on the day that tolbutamide therapy was instituted. Where the dosage exceeded this amount, insulin was gradually withdrawn by reducing the dose by 5-10 units per day. If symptoms and signs of ketosis appeared during this regime, tolbutamide was discontinued and the patient re-stabilized on insulin.

Blood counts, prothrombin indices, liver function tests and blood-urea estimations were carried out at frequent intervals. Protein-bound iodine and serum-inorganic-phosphorus estimations were performed on about half the patients.

The true blood sugar was determined by the method of King and Garner,[14] the serum cholesterol by the method of Pearson *et al.*,[15] the serum protein-bound iodine by the method of Meyer *et al.*,[16] the serum inorganic phosphorus by the method of Briggs,[17] and the serum potassium with an Eel flame photometer as described by Varley.[18]

The efficacy of treatment has been assessed according to our previous criteria[13] and the cases have been classified into 'good', 'fair' and 'poor' categories. The 'good' category consists of those cases in whom (*a*) insulin where used has been discontinued, (*b*) urine examinations at home and at the clinic have proved satisfactory, (*c*) blood sugars have been maintained at normal or near normal levels, and (*d*) the patients are feeling well and there are no side-effects. The 'fair' category consists of those patients in whom (*a*) insulin where used has been discontinued, (*b*) urine examinations at home and at the clinic have shown 0 to ++ glycosuria, (*c*) the blood sugar has not been maintained at normal levels but has been reduced appreciably, and (*d*) the patients are feeling well and there are no side-effects. The 'poor' category contains those cases who have shown little or no response.

RESULTS

'Good' Category. Control was good in 45 of the 105 cases (8 males and 37 females). The ages of this group varied between 43 and 77 years (average 61·9 years). The diabetes had been present from 3 months to 20 years (average 6·4 years); 13 of these 45 cases had been diabetic for 10 or more years. The age of onset of diabetes varied from 36 to 72 years. The group comprised 5 thin, 20 medium and 20 fat individuals. Patients with and without late manifestations of diabetes were included in this group. Of the 45 patients, 20 (44%) had been treated previously with insulin and the largest daily dose replaced by tolbutamide was 60 units (PZI 30 units + soluble insulin 30 units).

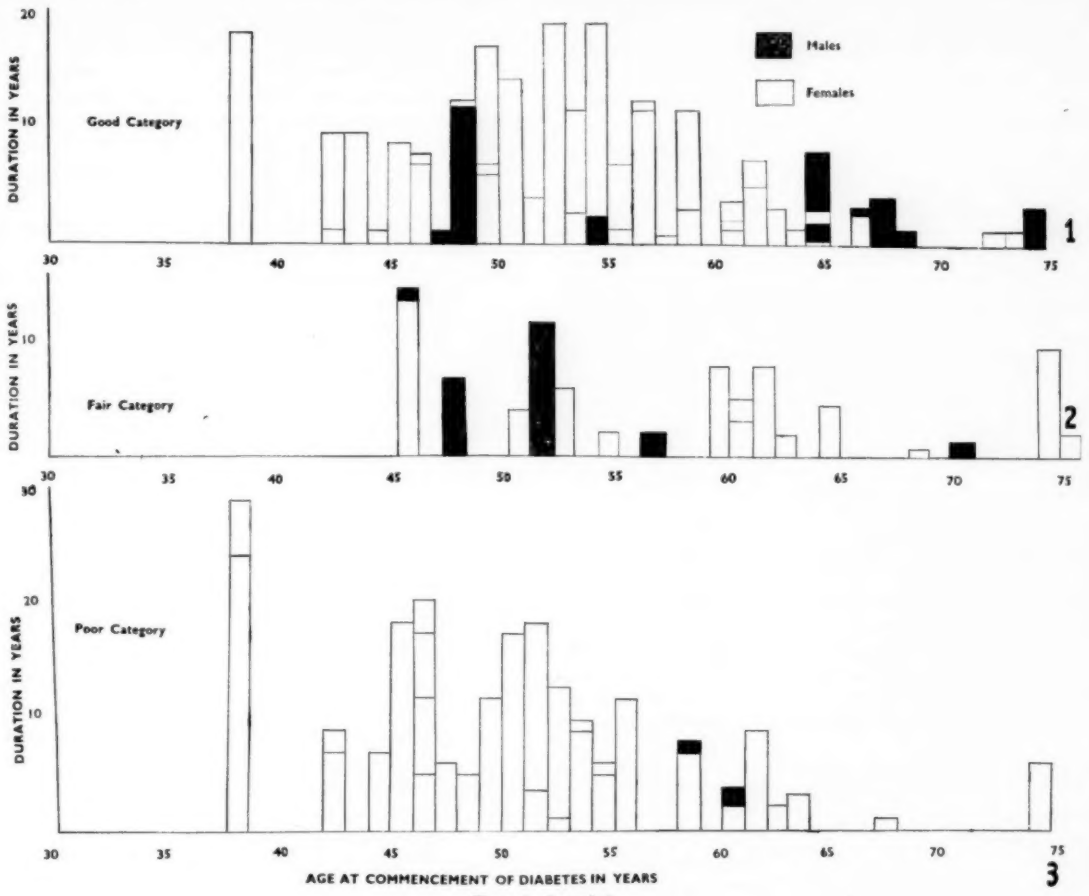
'Fair' Category. Fair control was obtained in 25 cases (6 males and 19 females). In this group the age ranged between 54 and 84 years (average 63·9 years), and the duration of diabetes from 2 months to 15 years (average 5·4 years). Body build was again variable, 4 patients being thin, 8 medium and 8 obese, and cases with and without late manifestations of diabetes were included. Of the 25 patients, 9 (36%) had been treated previously with insulin and the largest daily dose replaced by tolbutamide was 70 units of NPH insulin.

'Poor' Category. The control was poor in 35 cases (3 males and 32 females). The ages varied between 49 and 80 years (average 61·9 years) and the duration from 7 months to 30 years (average 9·8 years). Variation in body build was again noted, 6 patients being thin, 9 medium and 17 obese. Late manifestations of diabetes were present in some of the patients. Of the 35 patients, 23 (66%) had been treated previously with insulin. The age of onset varied from 38 to 74 years. Insulin dosage ranged from 0 to 60 units.

These results are demonstrated in Figs. 1, 2 and 3.

Change in Control

A change in control has occurred in 8 cases, all of whom were included in the series previously reported. Of 7 in the 'good' category, 5 have deteriorated to 'fair' control, and 2 to the 'poor' category, while 1 case under 'fair' control has now regressed to the 'poor' category. There have been several cases in our series who have felt so well while taking tolbuta-



Figs. 1, 2 and 3.

mide despite poor diabetic control that they have refused to discontinue the drug. Insulin has therefore been added to improve the control, but the dose has usually been less than that previously required.

Laboratory Investigations

The laboratory investigations did not reveal any gross abnormalities. The main haematological change noted was a frequent reversal of the neutrophil/lymphocyte ratio. This was not a permanent feature; all cases reverted to normality while still on treatment. The cause of this interesting phenomenon has not been ascertained.

In one case, a leucopenia of 2,900 per c.mm. (neutrophils 37% and lymphocytes 63%) occurred after a period of normal counts. Treatment with tolbutamide was continued and within 1 month the count had increased to 6,800 per c.mm. (neutrophils 44% and leucocytes 42%). The blood picture has remained normal during the past 4 months.

Alteration in liver function tests occurred in 2 patients during treatment. In one normal tests became markedly abnormal but no clinical change was evident; in the other an aggravation of previously abnormal tests occurred after an interval of 8 months.

Prothrombin indices were not affected.

The determinations of inorganic phosphorus, potassium, cholesterol and protein-bound iodine which were performed during treatment are shown in Table I. The phosphorus and potassium results showed no abnormality, except in one case where the potassium was raised. No cause for this was ascertained. There was little correlation between the cholesterol level and the degree of diabetic control. The serum protein-bound iodine values varied widely. A low serum protein-bound iodine result of 3·2 micrograms per 100 ml. was observed in one case and high values of 10·2, 14·0 and 16·0 μg./100 ml. in 3 patients. The high results may have been due to the ingestion of iodine-containing medicines. We were unable to demonstrate any depression of thyroid activity resulting from tolbutamide therapy.

TABLE I

Serum	*Mean*	*Range*	*Normal Values*
Inorganic phosphate	3·3 mg./100 ml.	1·8—4·4	2·0—4·0
Potassium	4·9 mEq./l.	4·1—6·4	4·4—5·1
Cholesterol ..	284 mg./100 ml.	170—450	120—250
PBI	6·2 μg./100 ml.	3·2—16·0	3·5—8·0

Side-effects

Side-effects were minimal. Two patients were unable to tolerate the drug because of nausea which supervened. Another case developed moderate angioneurotic swelling of the face.

A patient who had suffered a vitreous haemorrhage in the right eye while on 35 units of lente insulin, developed another haemorrhage in the left eye while on tolbutamide therapy.

A patient who was receiving 120 units of soluble insulin per day in 2 divided doses developed ketosis when the insulin was reduced and tolbutamide added. For a period of 1 week, while further attempts to control him were persevered with, he varied between hypo- and hyperglycaemia, and only returned to his normal control when the use of tolbutamide was abandoned. His previous dose of insulin was well able to control him and he has remained under good control since. This case emphasized the danger of using tolbutamide in patients requiring large doses of insulin.

DISCUSSION

Analysis of tolbutamide therapy in 105 diabetic cases reveals good control in 42·9% of cases, fair control in 23·8%, and poor control in 33·3%. Our results are in accord with the findings quoted by the workers of 3 leading British hospitals at the 11th Banting Memorial Meeting in July 1957,[19,20] who reported satisfactory control in 52% of their cases. The proportion of successful cases published by other authors varies enormously and is dependent to a large extent on the choice of patients and the criteria adopted for assessing adequate control.

The patients selected for treatment were all over the age of 43 years and the majority over 60. Previous workers have shown that this age-group responds most satisfactorily to tolbutamide and that the drug usually fails in the younger insulin-deficient diabetic. However, it must be noted that the youngest age at onset in the 'good' category was 36 years, and that 29% of these cases had been diabetic for 10-20 years.

Most of our patients were between medium and obese and only 14% could be classified as thin. The majority of workers in this field are agreed that obese diabetic patients should be treated with dietary restriction only, as this measure will achieve adequate control in a large percentage of cases.[21] However, tolbutamide has a definite advantage in the treatment of those obese patients in whom dietary restriction fails. It must be emphasized that these patients should be warned not to become careless over their diet. Such negligence will lead to further gain in weight and deleterious effects on the patient's health. In contrast, tolbutamide may be of great value in the treatment of elderly thin diabetics who are unable to regain their normal weight. We have found that tolbutamide will maintain good control when these patients partake of a more liberal diet.

The usual maintenance dose of tolbutamide has been 1·0 - 1·5 g. per day. Where control has not been adequate this has been increased up to 3 g. per day with slight improvement in a few cases.

Some workers have suggested that nausea is less likely to occur if the drug is administered after meals. In this series, however, no difference has been noted whether the drug was given before or after meals.

Although effective control is often achieved within the first week of administration, it is advisable to persist for at least 3 weeks, because the optimal effect may be delayed.

No serious toxic effects have been noted during tolbutamide administration, in contrast to the fatalities reported during the treatment with carbutamide. Moreover, side-effects have been minimal. Two of our patients were compelled to discontinue the drug on account of nausea, and one patient as a result of angioneurotic oedema. Similar side-effects have been reported by other workers.[22-24]

We have been particularly concerned with blood changes which might occur during treatment. The most constant change found was that of a reversal of the neutrophil/lymphocyte ratio. This change was always temporary and occurred in 9 of the 'good', 20 of the 'fair', and 8 of the 'poor' cases. No explanation for this has been found, and it will be necessary to do a similar series of blood counts on a control group before it can be associated with the administration of tolbutamide.

Severe leucopenia developed in 1 case in our series (2,900 leucocytes per c.ml.), but this disappeared in spite of continuing the tolbutamide in unchanged dosage. Stötter[24] found a reduction of leucocytes in some cases of tolbutamide-treated diabetics, but found similar reduction in cases treated with insulin.

The alteration in liver function tests found in several of our cases during treatment cannot be considered as having special significance in view of the common occurrence of abnormalities in liver function tests during the course of diabetes.[25]

Clinically no symptoms or signs were noted to suggest any liver dysfunction during the course of tolbutamide administration.

Protein-bound iodine estimations have not revealed any alterations in thyroid function.

Infections, injuries and operations may disorganize diabetic control and it has been found that tolbutamide, even in increased dosage, is unable to control the resulting hyperglycaemia and ketosis. Insulin is then required as an emergency measure. Several of our patients in the 'good' category have been successfully controlled while undergoing cataract operations under local anaesthesia; the tolbutamide has maintained adequate control during the operative and post-operative period.

The presence of ketosis constitutes a definite contra-indication to the use of tolbutamide and it must be emphasized that it is dangerous to continue with the drug in its presence.

Amongst our cases who were originally reasonably well controlled, 8 have now deteriorated and stabilization is unsatisfactory. Other workers have reported similar experiences.[8, 24] The cause of this phenomenon has not been elucidated. It is possible that the therapeutic effect of the drug may diminish after a period. However, a more likely explanation is that the patients adhere less strictly to the prescribed diet; we have noted that gain in weight has often accompanied deterioration in control.

We have used a combination of tolbutamide and insulin in a few patients who did not respond to tolbutamide alone. These patients have required a smaller dose of insulin, but it is

doubtful whether the addition of tolbutamide has any advantage over routine insulin therapy.

It is premature to speculate on the effect of tolbutamide in preventing the late manifestations of diabetes. This will require careful follow-up studies over many years and comparison with insulin-treated cases.

SUMMARY

1. 105 diabetic out-patients with an average of 61 years were treated with tolbutamide.

2. Good control was obtained in 42·9%, fair control in 23·8% and poor control in 33·3%.

3. No toxic and only minimal side-effects were encountered.

4. A temporary reversal of the neutrophil/lymphocyte ratio was found in 37 cases.

5. Deterioration in control has occurred in 8 patients after several months of tolbutamide therapy.

6. The long-term effect of tolbutamide cannot be assessed at this stage.

Our grateful thanks are due to Sister D. E. Maxwell and Staff Nurse E. Smit for their loyal cooperation. We are indebted to Dr. I. Bersohn, Dr. H. B. W. Greig and Miss E. Hallendorff of the South African Institute for Medical Research for their technical assistance, and to Mr. A. M. Shevitz for the reproduction of the three graphs.

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TOLBUTAMIDE (ARTOSIN, RASTINON, D 860) IN DIABETES *

CLINICAL TRIALS CONTINUED

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We have previously reported our preliminary findings with tolbutamide based on a short-term trial in 73 patients,[1] some of which have been modified and extended by further experience. For discussion of the chemical aspects of the substance and of its mode of action the reader is referred elsewhere. The object of this paper is simply to record our results up to the end of June 1957 and to make certain recommendations based upon them. I shall try particularly to indicate where our approach or findings differed from previous reports.

THE PATIENTS

We have records of 250 patients who have been treated with D 860 (tolbutamide), some in the wards and some in the diabetic clinic. In the latter the patients have been seen as far as possible at weekly intervals and have had regular blood-sugar estimations then performed (usually fasting). All blood sugars were determined by a modified Hagedorn-Jensen method. Weekly 24-hour urine collections have been analysed for sugar in some cases; in others a note has been made by the patient of his own tests throughout the week; in a few, repeated glucose tolerance tests have been carried out.

The dosage of D 860 in most cases has been 1 g. (2 tablets) daily; in several the maintenance has been higher, up to 3 g. Only in special cases in hospital have higher doses been tried. It is not feasible to analyse our results separately into different dosage groups, but there is certainly very little difference between the effects of 1 g. and of 3 g. If a patient does not respond at all to 1 g. he is very unlikely to respond to 3 g., though he may respond somewhat better to the larger dose.

Incidentally tolbutamide is less cumulative than carbutamide (BZ 55) and should be given in divided doses, 2 or 3 times daily.[2] It is perhaps best to take the drug after meals so as to prevent the nausea which it occasionally produces.

The change-over from insulin to D 860 seems to us very important for a scientific assessment of response. Whenever possible, where no risk was thought to be involved, insulin was stopped completely for some time before D 860 was started. In this way a real base-line control could be established. In a surprisingly large number of cases where insulin had been stopped, the patient remained as well controlled as before, or even better, so that D 860 was unnecessary. Had it been used either with or immediately replacing insulin it would have got the credit for this improvement quite erroneously and the patients would have continued getting unnecessary treatment. Several patients were found to be much better controlled after insulin had been stopped than they had been before they had originally started insulin—clearly suggesting a real 'curative' or at least alleviating effect of insulin! This finding further suggests that a review of all 'mild' diabetics on insulin, with a view to omitting this drug where possible, might prove most salutory and rewarding, quite apart from the use of D 860

* Presented at the South African Medical Congress, Durban, September 1957.

Case F.F. A Coloured female of 69, with mild diabetes of 2 years' duration, had been taking 20-24 units of lente insulin daily. Her urine always contained sugar (+ to +++) and our last record of her blood sugar was 163 mg. per 100 ml. fasting and 255 mid-morning. Insulin was stopped, her urine became sugar-free, and mid-morning blood-sugar readings of 130, 151 and 195 have been obtained.

Certainly, however, this method of change-over should not be used in the 'severe' or doubtful diabetic where, if D 860 is to be tried at all, it must first be added to insulin or the latter slowly decreased. We have made one error in this connexion!

Case M.W. A 50-year-old non-obese European female who had been diabetic for 2 years was taking 28 units of lente insulin daily. After omitting insulin she was admitted to hospital 4 days later in severe ketosis. This is the only instance in which any serious difficulty has arisen in the trial.

Since it is well known that the severe ('growth-onset', ketosis-prone, insulin-requiring) diabetic is most unlikely to respond to D 860 at all, such cases will be considered separately from the older, mild ('maturity-onset', frequently obese) group.* We have also separated an 'intermediate' group, members of which were in the older age-group but developed severe diabetic symptoms with marked loss of weight when deprived of insulin. It must be realized that some older people may actually have the severe, 'young' type of diabetes (e.g. case M.W. above).

RESULTS

The response to D 860 is graded as excellent, partial or negligible. 'Excellent' indicates that an absence of glycosuria, and blood sugars within the normal range, were obtained—in many of the 'partial' responses control of the diabetes could be considered adequate.

Type of diabetes (Table I)

As expected, of 15 'severe' diabetics in whom D 860 was tried in doses up to 12 g. a day, none responded well. In one there was a partial, but very incomplete, response while in 3 the control was at least temporarily improved by D 860 used in conjunction with insulin. Of the 14 'intermediate' diabetics, 3 responded extremely well. There were 200 'mild' cases, of which 21% had an excellent response, while 29·5% failed to respond.

TABLE I. TYPE OF DIABETES AND CONTROL WITH D 860

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
Severe	0	4*	11	15
Intermediate ..	3	1	10	14
Mild	42 (21%)	99 (49·5%)	59 (29·5%)	200
'Steroid' Diabetes ..	1	0	1	2
Chronic Pancreatitis	0	2	4	6
Insufficient data for classification ..	—	—	—	13
				250

* In combination with insulin in 3 cases.

There were 2 cases of steroid diabetes, one of which responded very well to D 860 (much better than to 80 units of insulin), while one failed completely to respond to 6 g. a day. In both cases the diabetes became latent after the corticosteroid therapy was stopped. (This variability of response presumably accounts for the discrepancies in the literature on the subject of D 860 in steroid-induced diabetes.)

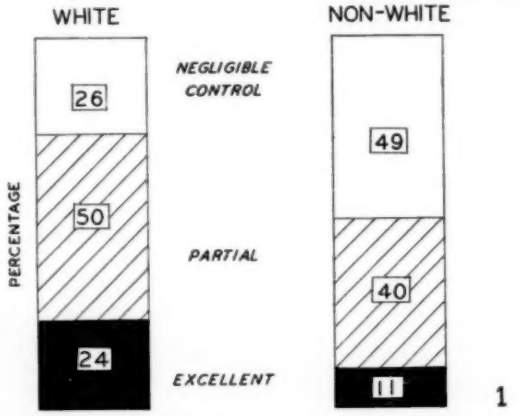
Of the 6 cases of proven chronic pancreatitis, 4 had the typically severe diabetic syndrome, and D 860 was of no value even in large doses; 2 had much milder and more recently developed diabetes, and in them D 860 achieved partial control.

Sex, Race and Age

The following further analyses refer solely to the 200 'mild' diabetic patients:

Sex. There were only 45 males, as opposed to 155 females, in the series. No significant difference in response was found between the sexes.

Race (Fig. 1). There were 45 Coloured and African patients among the 200, and it was surprising that they did distinctly



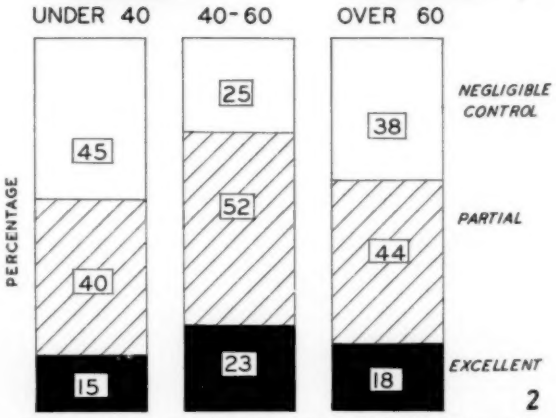


Fig. 1. Control with D 860 in White and non-White mild diabetics.

Fig. 2. Control with D 860 according to age of onset in mild diabetics.

* There has been some confusion concerning the terms used to distinguish these two groups of diabetics. It should be noted that 'severe' and 'mild' bear no relation to the amount of insulin which the patient may be taking. The 'severe' diabetic will always need some insulin; the mild diabetic may be taking none or 100 units. Some mild cases, as the German writers have stressed, are relatively insulin-resistant, and these may respond well to tolbutamide. The 'mild' diabetic does not go into ketosis even when untreated.

less well on D 860 than the Europeans. Thus 49% of them completely failed to respond, as compared to 26% of Europeans. Further analysis of the White and Coloured patients failed to uncover any particular distinction between the groups which might tend to produce such a difference of response. Among the non-Whites were 4 African Bantu, 2 of whom responded extremely well. Our results seem to indicate that D 860 is of less value in Coloured people in Cape Town than in Whites.

Age. All the mild diabetics were over 40 except for 5, in 3 of whom partial control was attained on D 860. Analysis revealed almost exactly the same percentage responses in the 40-60 and in the 60-80 age-groups. Of 3 patients over 80, 2 failed to respond at all.

Age at onset of diabetes

Our figures suggest (but do not prove) that the age-of-onset group 40-60 respond best (Fig. 2).

Length of time diabetic (Table II)

49 of our patients had been diabetic for more than 10 years, including 17 for more than 20 years. The proportion of this group whose response was excellent was actually *higher* than in the whole series, although there was also a higher percentage of complete failures.

TABLE II. LENGTH OF TIME DIABETIC AND CONTROL WITH D 860

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
10-20 years diabetic	8 (25%)	9 (28%)	15 (47%)	32
Over 20 years diabetic	6	7	4	17
Total over 10 years diabetic	14 (28%)	16 (33%)	19 (37%)	49

Body size

We have divided the mild diabetics into 3 groups—obese, medium and thin. To our surprise, as Fig. 5 indicates, the obese group (55 patients) actually responded less well to D 860 than the others. It was gratifying to find that the response of the 23 thin patients was so good, and this suggests that, provided the lean, 'severe' type of diabetic is excluded, the *mild* lean diabetic does as well as the obese diabetic, or better. We feel that this lean diabetic is particularly the one who needs 'tablet' therapy, as opposed to the obese diabetic, who needs dietary restriction. Among this lean group were 7 who were put onto a completely free diet and actually encouraged to 'eat everything'; of these, 6 gained weight (Figs. 3 and 4), which they had previously been unable to do;

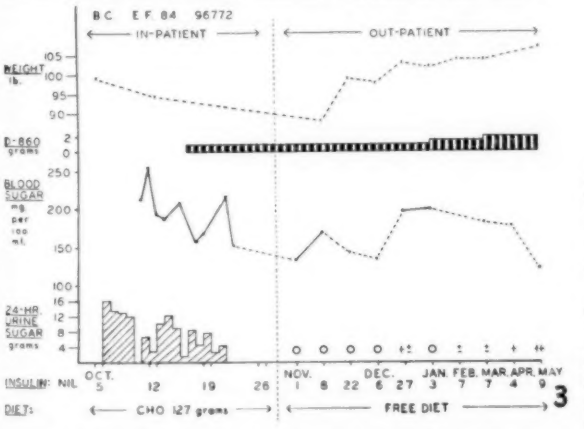


Fig. 3. B.C. A very thin old lady, in whom weight gain was accomplished on a free diet, while maintaining fair control of diabetes with D 860.*

* In all figures the sex, race, and age of the patient are shown at the top. F.B.S.=fasting blood sugar.

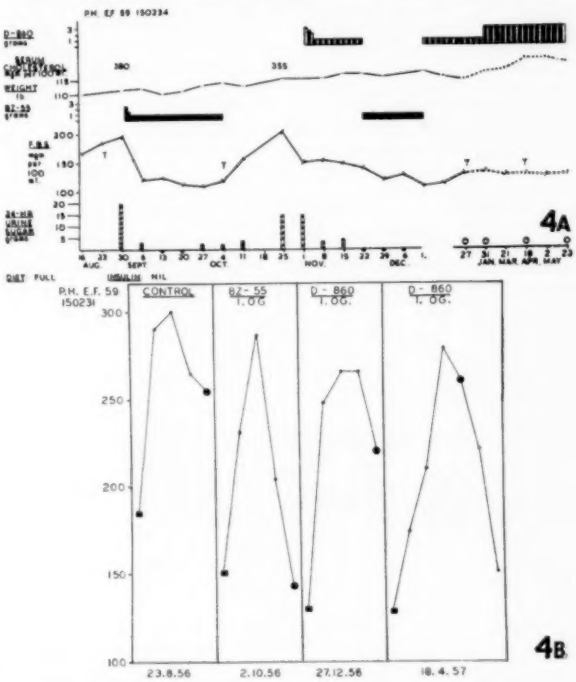


Fig. 4. P.H. (*a*) This thin woman was able to gain weight on D 860 with a free diet. (*b*) Glucose tolerance curves (at points marked T in Fig. 5*a*) show reduction of fasting levels on D 860 and BZ 55, but persistence of abnormally high curve (e.g. diminished sugar tolerance). Fasting and half-hourly blood-sugar levels after 50 g. of glucose orally are shown as dots, with heavy dots for fasting and 2-hour readings.

3 of the 7 were excellently controlled on D 860 despite their free diet, and in 4 the control was partial or good. There seems no reason to restrict the caloric intake of a diabetic who can be well controlled on oral therapy and who is very underweight.

Prior insulin treatment

Of the 200 patients, 111 had been taking insulin before D 860 was started. The length of time over which insulin had been taken appeared to have little effect on the likelihood of response to D 860, although there was some rise in the proportion of patients who completely failed to respond as the length of time increased.

There was little correlation between the size of the insulin dosage and the likelihood of response, except that the percentage failing completely was rather higher in those

taking over 40 units a day (48%). Actually an excellent response was seen in a higher proportion of patients who had received insulin (24%) than in those who never had (19%).

There were 4 patients who had been taking 100 units of insulin or more daily before D 860 was tried. Two had a partial response on D 860 alone (both were better controlled by this than they had been on 100 units of insulin!), and 2 had no response.

Change in body weight on D 860 therapy (Fig. 6)

We have been struck with the frequency with which patients have gained weight on D 860, despite the fact that they were supposed to be on a restricted diet. Far fewer lost weight, which is what was expected of them. There may be psychological reasons for this, and we have no control series *not* on

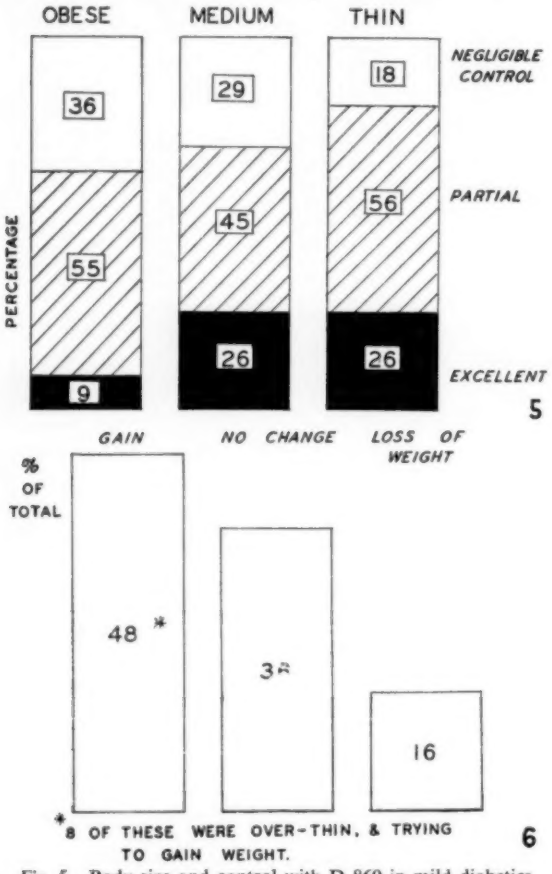


Fig. 5. Body size and control with D 860 in mild diabetics.
Fig. 6. Indicating change of more than 3 lb. in patient's body weight after 3 months on D 860.

D 860; so that this finding is not necessarily significant. Nevertheless nearly 50% of our patients who were watched for more than 3 months definitely gained weight (see Fig. 7).

Long-term action of D 860

We have records of 37 patients who have been taking D 860 for more than 6 months (Figs. 3, 4, 7 and 8). In 13 of them

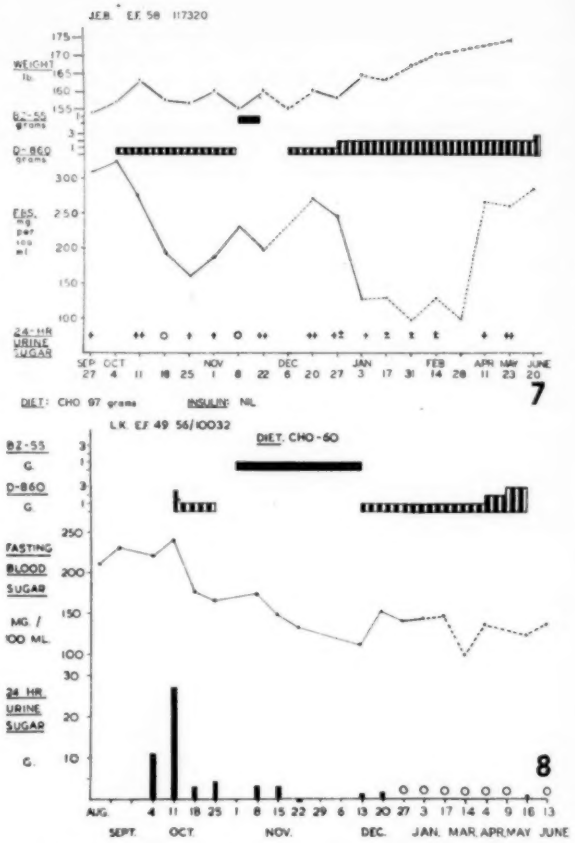


Fig. 7. J.E.B. Good initial effect, wearing off. Improvement with increased dose, again wearing off. Note weight gain.
Fig. 8. L.K. Reasonably good, maintained control; not improved by increased dosage.

there has been a definite diminution in its effectiveness (e.g. Fig. 7). In some the response has been improved by increasing the dose, and none have yet returned to insulin, but some may need to do so later. In general we have not found 3 g. to be more effective than 1 g., although 0·5 g. is frequently found to be a submaximal dose.

Diabetic vascular complications and control

In our series 15 patients had marked retinopathy, and of them only one had an excellent response. The presence of diabetic complications otherwise did not appear to affect the likelihood of response to D 860.

Toxicity of D 860

A few patients complained of nausea, dizziness, tiredness, and 2 patients of vomiting shortly after starting the tablets. These symptoms later passed off and it is difficult to assess their true relationship to the D 860. There were 4 patients who developed rashes; 3 of them were mild (purpuric in one, urticarial in one, papular in one) and soon passed off; the 4th was more severe.

Case C.S. A Coloured female aged 50, with mild diabetes of recent onset, was put onto 3 g. of D 860 a day in place of 40 units of insulin. In 2 weeks a very severe stomatitis appeared, which did not clear up until D 860 was stopped. The blood count was normal. An itchy purpuric rash also occurred on the arms and legs, and later this rash was twice caused to reappear some 12 hours after single gram doses of D 860.

This was the only case in which D 860 had to be discontinued because of its toxic effects. We have seen no depression of leucocyte count.

Pregnancy

D 860 can be used during pregnancy. Two pregnant patients are at present well controlled with it.

Times of 'stress'

Patients on D 860 may require insulin if they develop infections or undergo other 'stress'. On the other hand, D 860 may well prove very useful in patients undergoing operation, since the danger of hypoglycaemia is obviated and catheterization and intravenous glucose are less necessary. We have seen instances of both these states of affairs.

Speed of action and effect of discontinuance of D 860

In patients who were well controlled on D 860, a relapse has occurred in every instance where it has been omitted. Occasionally the relapse appears rapidly, as in one patient in whom glycosuria was repeatedly found the same day when no tablets were taken and in whom it equally rapidly disappeared when the tablets were taken again. Others did not relapse for one or two weeks. We have no evidence that D 860 is curative.

The hypoglycaemic effect of D 860 was mostly seen within three or four days of starting treatment, sometimes more rapidly, and sometimes not for two or three weeks. Because of this it is probably worth continuing a trial of this drug up to 3 weeks where practicable. Since D 860 may be to some extent cumulative (though less so than BZ 55) a loading dose of 3 g. the first day, with gradual reduction, is often used.

Blood-sugar level on D 860

D 860 appears to act largely by reducing the fasting blood-sugar level, but it has much less affect on the actual tolerance to glucose. We have several times found patients with normal fasting levels but abnormally high postprandial blood sugar, while others with normal fasting sugar showed very high 1-1½ hour figures on glucose tolerance tests (Fig. 4*b*). Too much reliance, therefore, should not be placed on the fasting sugar as the sole test of response to D 860.

Hypoglycaemic symptoms due to D 860 alone are rare and mild. We think we have seen such symptoms in 3 patients, but have not proved this. In such cases the patients may be more comfortable after halving the dosage of D 860. When it is given with insulin, hypoglycaemia should be watched for, since occasionally the effects of the two antidiabetic agents appear to be additive.

Use of D 860 *and insulin together*

Because of our method of change-over from insulin to D 860 we have not very much experience of the use of the two together, nor do we believe that this will often prove helpful. It seems to us that insulin or D 860 alone almost always provides as good control as a combination. Where D 860 is given to a mild diabetic already on insulin and a better result is obtained, it will usually be found that insulin is unnecessary.

Recommendations concerning the use of D 860 *in general practice*

1. It should never be used in the severe young diabetic, nor in any diabetic who has ever been in ketosis.
2. The obese diabetic should be treated in the first instance by a reducing diet.
3. D 860 may safely be tried in a mild diabetic who is not on insulin, who still has glycosuria and hyperglycaemia despite a low carbohydrate diet, and who has no ketonuria.
4. It is not always easy to know in which diabetics it is safe to stop insulin. In general practice it would be safer either not to use D 860 in diabetics already on insulin *or* to use it only in addition to insulin in patients who are poorly controlled on insulin alone and then, if control is improved, slowly to reduce the insulin. We would not recommend changing from insulin to D 860 in any patient whose diabetes is well controlled in general practice.
5. Adherence to dietary regime is still necessary, though, as indicated in this paper, it may be considerably relaxed in the thin diabetic who is controlled on D 860.

CONCLUSIONS

1. In general, like everyone else we find that the severe diabetic is unsuitable for D 860; certainly unless admitted to hospital for special observation.
2. D 860 is effective in a high proportion of patients whose diabetes started over the age of 40 and who are of 'mild' type. Otherwise we can see no very definite correlation between likelihood of response and age, sex, length of diabetic history, previous insulin dosage, time, presence of complications, or body weight. Apparently Coloured people respond less well on the whole, but *in any mild case the only way to know if a patient will respond to D* 860 *is to try.*
3. German workers[3] have reported close correlation between age and response to D 860, as well as between age of onset and response, and between increasing body weight and response; and a negative correlation between prior insulin dosage and response and between length of time insulin had been used and response. Some of the differences between their conclusions and ours may be because they have not separated their severe from their mild cases, so that some of their series are automatically weighted on the side of youth, big insulin dosage, and leanness, with correspondingly poor response in these groups.
4. We repeat our belief that obese patients should primarily be treated by dietary restriction and not with insulin or D 860, except in emergency. On the other hand the lean mild diabetic may be very suitable for D 860 and perhaps for an increase in diet.
5. *To summarize*, then, the particular value of D 860 appears to be
   (i) in the mild thin diabetic,
   (ii) in other mild diabetics in whom diet alone does not produce sufficient control, and
   (iii) in mild diabetics perhaps especially at the time of an operation.
   (iv) It should be of special value to obviate the danger of hypoglycaemia in mild diabetics with high or low renal thresholds.

(v) Similarly in patients suffering from angina, myocardial infarction or peripheral vascular disease, where hypoglycaemia is to be avoided, D 860 should be safer than insulin.

(vi) In patients who are stupid, or are subject to unpleasant hypoglycaemia, or insulin allergy or atrophy, D 860 may be particularly valuable.

SUMMARY

The results of the use of D 860 in 250 diabetic patients at Groote Schuur Hospital are presented. Certain conclusions are drawn and recommendations made on the basis of this analysis.

The D 860 used in this trial was largely supplied as 'Rastinon' by the Newport Trading Corporation of Johannesburg. Latterly some 'Artosin' has been given to us by Noristan Laboratories of Pretoria. We are very grateful to both of these firms.

I thank herewith all physicians associated with this trial at Groote Schuur Hospital, especially the other members of the Diabetic Clinic, and most especially Prof. G. C. Linder.

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THE TREATMENT OF INTRACTABLE PAIN*

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The rapid increase in medical knowledge which has taken place during this century has brought with it not only specific forms of treatment, but also a clearer appreciation of the physiological and pathological states with which we are confronted. Symptomatic as well as specific treatment has therefore benefited and become more rational and effective. In fact almost every advance in medicine has had some bearing, direct or indirect, on our management of the common and urgent symptom of pain.

My intention in this article is to discuss the effect of hormones, with or without cytotactic drugs, some aspects of deep X-ray therapy, and the adjuvant action on morphia or its substitutes of some recently available drugs, in certain conditions where pain dominates the clinical picture.

THE STEROID HORMONES

All will agree that the steroid hormones, with their powerful and widespread effects, should be used as pain killers on rare occasions, and then only when the therapeutic problem is clearly understood. There are, however, circumstances when their use as a pain killer is justified.

The condition for which the adrenal steroid hormones were first widely used gives us an example, as the severity of the pain in acute rheumatoid arthritis may well enforce the temporary use of cortisone in the full knowledge that its analgesic effect must be paid for by the troubles of withdrawal, and possibly the development of side-effects.

Gout is another example of a cortisone-like substance being welcomed simply for the control of pain which it affords when other measures have failed. Its use will be purely symptomatic as it will have no curative effect, and in fact will produce a relapse when it is withdrawn. The relief of pain may, nevertheless, be quite dramatic, and relapse can be prevented by continuing with colchicine after stopping the cortisone.

A less well known example of pain controlled by steroid hormones is provided by cranial arteritis, in which the pain may be both severe and baffling from the diagnostic point of view. The vertical, temporal or occipital pain of a persistent character about which an elderly patient may complain with an intensity which compels attention is familiar in this condition, but a paroxysmal pain is more unusual.

A man of 72 was recently seen complaining that for a month he had an agonizing pain starting behind the right eye and spreading to the right side of the forehead and cheek. The pain was of great intensity, lasting 30 to 45 minutes, and was burning in character. There were no abnormal physical signs and he was a poor witness but his story had a genuine ring, and he insisted that the pain was produced when he got his head into a certain position. He demonstrated this by lying back on his pillows with his face turned to the right, and at once jumped up in obvious agony.

Many diagnoses were considered, including the correct one, but this was only firmly established when tenderness and thickening of the right temporal artery appeared at the same time as he experienced partial loss of vision in the eye on that side. Cortisone entirely relieved his pain and he has made an excellent recovery apart from the partial loss of vision. Before reaching the correct diagnosis his outlook appeared to be bad, for his pain was agonizing and uncontrolled without large doses of powerful analgesics.

STEROID HORMONES AND CYTOTACTIC DRUGS

The steroid hormones and corticotrophin, in combination with alkylating agents, may be effective in temporarily controlling pain from widespread metastases, including those in the liver and lungs. This form of treatment is worth considering in a patient suffering from an advanced stage of carcinomatosis when the primary growth is pancreatic, gastric, renal or colonic. It can also be tried for widespread secondaries from the breast or prostate when gonadectomy and sex hormone treatment have been used and their effect is waning. Steroid hormones and cytotactic drugs should

*A paper read in a symposium on the Treatment of Pain (opened by Sir Russell Brain, Bt.) at the South African Medical Congress, Durban, September 1957.

however be used with caution when moniliasis is present or develops in already debilitated patients.

Triethylene melamine is an alkylating cytotactic drug which can be taken by mouth. A total of 0·1 to 0·2 mg. per kg. is given in divided doses over a three-day period, and may be combined with 40 units of corticotrophin gel, which should be given twice daily for a few days before and during the treatment.

Nitrogen mustard in similar dosage and combination with corticotrophin can be given by injection. A convenient means of doing this is to inject it into a fast running intravenous drip of 5% glucose, in three doses at intervals of 48 hours.

The value of the adrenal steroids may be that they supplement the lympholytic action of the nitrogen mustard, and they may also have a protective action upon the blood-forming organs (Lemon, 1956). The latter is of great importance, as the possibility of using this form of treatment depends on reasonably normal activity of the bone marrow, with adequate leucocyte and thrombocyte production. It can therefore only be carried out with reasonable safety when adequate haematological control is available. The period of relief achieved may not be more than one or two months, but that may be sufficient to spare the patient severe pain up to the time of his death.

Adequate haematological control is also obviously of first importance when patients with a reticulosis such as Hodgkin's disease or follicular lymphoma are undergoing treatment with some form of mustard preparation.

Gross discomfort is commoner than severe pain in the reticuloses, but the distinction may be a fine one, and valuable relief may be obtained by reducing local pressure. This is usually done by deep X-irradiation, but chemotherapy may be of some value when the apparatus is not readily available, or when a patient already far advanced in disease wishes particularly to remain in or near to his own home. Chemotherapy also has a part to play when large local skin doses of deep X-rays have already been given.

Triethylene thiophosphoramide, or Thiotepa, is a useful mustard preparation in the reticuloses as it can be given by mouth or by the intravenous or intramuscular route and is not locally irritating. An initial dose of 5 mg. by injection on alternate days, or 10 mg. by mouth daily, is adjusted by the response of the blood count, which should at first be estimated daily. The total amount given in a course will vary according to the blood count between the approximate limits of 75-225 mg. and may be preceded or accompanied by a steroid hormone, such as prednisolone, 10 mg. three times a day.

Very severe pruritus can occur in Hodgkin's and allied diseases, and be both intensely distressing and exhausting to the patient. It may, however, respond to antihistamines and steroid hormones in combination, and this is a real advance in symptomatic treatment.

ANTIMETABOLITE DRUGS

As in the reticuloses, pain is not a particularly common symptom in the leukaemias, but at times the misery from the condition of the mouth in acute leukaemia may be almost unendurable. It is then that the only real relief, albeit temporary, may be from some antimetabolite drug, with or without corticotrophin or cortisone. The most useful of these drugs at present is 6-mercaptopurine, an antipurine antimetabolite with practically no toxicity (Galton, 1957). It is given in initial daily doses of 2·5 mg. per kg., the subsequent dosage being controlled by the white blood and platelet counts. In practice the treatment has to be continued until the marrow is aplastic if it is to have any hope of producing a real effect.

Corticotrophin or cortisone can be given with the 6-mercaptopurine, and are especially necessary as the marrow becomes increasingly hypoplastic.

Amethopterin, a folic acid antagonist, is the most useful drug in children, but will itself cause severe ulceration of buccal mucosa and the gums. It does not, therefore, give symptomatic relief quickly, but in conjunction with the steroid hormones may lead to remission of the leukaemic state for several months.

The spleen in chronic myeloid leukaemia is occasionally a source of great discomfort, or even of severe pain if perisplenitis develops and persists. Once again deep X-irradiation is the treatment of choice, but Busulphan (Myleran) in 2 mg. doses, three times a day, continued until relief is achieved or the white blood count falls to a normal level, can be used in the patient's home with all the attendant advantages in the way of maintaining morale and some sense of happiness.

THE SEX HORMONES

Gonadectomy has long been practised for the relief of metastases, chiefly in bone, when the primary growth is in the breast or the prostate gland, and further value was added to this procedure when the oestrogens and testosterone came into use. The control of the extragonadal secretion of sex hormones is the object, and since the advent of cortisone as replacement therapy, adrenalectomy and hypophysectomy have become possible and on occasions are effective means of achieving this. It is usual to begin the treatment by using sex hormone therapy alone. Oestrogen, in the form of stilboestrol, or chlorotrianisene (Tace), is used in the case of cancer of the prostate, and testosterone for cancer of the breast. Eventually, however, tolerance is acquired and gonadectomy has to be considered. This relatively simple procedure, together with sex hormone administration, may result in a further period of remission, but if this combination fails or relief is short-lived, the difficult decision about further operative treatment must be faced unless some alternative can be found.

A possible alternative is at present under trial at various centres and consists of destruction of the pituitary gland surgically or by an implantation of radio-active gold or yttrium. Mr. Geoffrey Bateman has kindly given me permission to report the results he has so far obtained at St. Thomas's Hospital.

His surgical approach to the pituitary fossa is trans-septal. Sub-mucous resection of the nasal septum is carried out and the sphenoidal sinus is opened. The septum dividing the cavity into two is removed and the downward bulge of the pituitary fossa identified in the roof of the cavity. A probe is introduced against this bulge at an angle previously determined by radiographs, and its exact position established with the help of an X-ray image intensifier. The floor of the pituitary fossa is then punctured at this point and a seed or seeds of the radio-active element implanted.

Optic atrophy has recently been observed following the use of radon seeds or radio-active gold grains in the pituitary, and it is in an attempt to avoid this that radio-active form of the element yttrium has come into use. Yttrium (^{90}Yt) has a short half-life (61 hours), similar to that of radio-active gold, but unlike ^{198}Au its emanations are pure beta rays with an intense local reaction. Radio-active gold, on the other hand, has both gamma and beta irradiations, and it is the former which prove a hazard to the optic chiasma. Mr. Bateman has done a trans-septal hypophysectomy on 12 patients with secondary deposits from carcinoma of the breast. Four of these showed improvement and 8 no improvement. His figures for radio-active gold implantation are similar, namely 11 cases, of which 4 were improved and 7 not improved.

At the time when this paper was completed he had implanted yttrium into the pituitary of 3 patients, 2 of whom had improved and 1 had not improved. One of the two cases showed an improvement sufficiently striking to deserve special mention. Professor J. B. Kinmonth, who suggested to Mr. Bateman that he should develop this work, has kindly given permission for this.

Mrs. M., aged 47, was admitted to St. Thomas's Hospital under the care of Professor J. B. Kinmonth on 18 March 1957, with a stage 4 carcinoma of the right breast. She had noted a lump 3 years before and it had slowly enlarged. For 8 months the right nipple had been ulcerated and for 3 months she had had a cough with some sputum and had been short of breath.

On examination she had a hard mass in the right breast behind the nipple, which was affected by Paget's disease (Fig. 1). The mass was fixed to the skin and to the deep tissues, and there were secondary glands on the right side of the neck and one fixed in the right axilla. The X-ray of her chest showed extensive secondary deposits in both lung fields (Fig. 5a). There were no bony deposits demonstrable radiographically.

Mr. Bateman implanted 4 yttrium pellets, using the technique I have mentioned (Figs. 3 and 4). An effect on the pituitary was demonstrated by radio-active iodine studies, which showed a thyroid uptake of 55% before operation, and only 5·6% after the operation. The patient also developed vomiting and a fall in blood pressure 20 days post-operatively.

Fourteen days after the operation (17 April 1957) the primary growth was half its original size (Fig. 2), the fixed axillary gland had gone and the ulceration of the nipple had healed (Fig. 5b). All the glands in the neck had disappeared except for one which was half its original size. X-rays of chest showed marked improvement, all the secondaries being smaller (Fig. 5b).

She was discharged on 7 May with further improvement in the chest X-ray appearances, taking 25 mg. of cortisone twice a day.

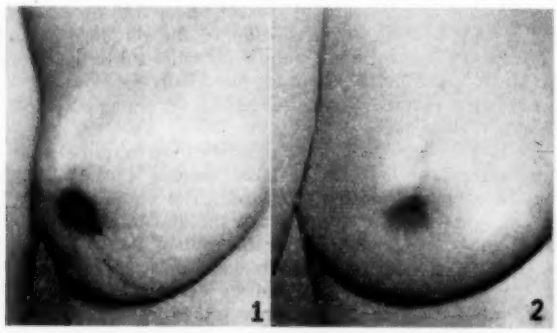
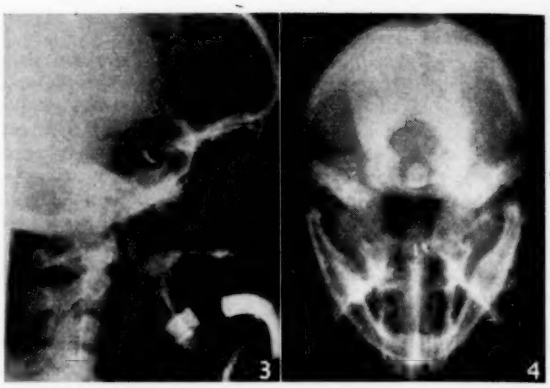


Fig. 1. Carcinoma of breast before treatment.
Fig. 2. Same case after treatment.



Figs. 3 *and* 4. Yttrium seeds in position.

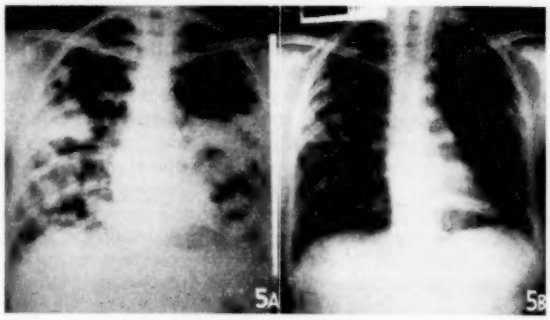


Fig. 5*a*. X-ray of chest before treatment.
Fig. 5*b*. X-ray of chest after treatment.

On 3 June, 2 months after operation, no glands were palpable, no mass was found in the breast, the nipple had healed and she was gaining weight. She had, however, a little trouble from diabetes insipidus.

This is only a single case of treatment with ^{90}Yt, but the result so far is remarkable.

Another alternative to radical surgery is presented by the possibility of suppressing pituitary and adrenal function by the use of cortisone. This method is better adapted to dealing with metastases from the breast than from the prostate, as cortisone is partly metabolized to androgens and thus supplies an unwanted hormonal stimulus to secondaries from a prostate growth, whereas its products have no oestrogenic activity. Lemon (1956) reports from his clinic that so far the results of treating patients with carcinoma of the breast with pituitary and adrenal suppression by cortisone in women who have been castrated are not significantly different from the results he has observed from hypophysectomy or adrenalectomy. He advocates the use of dried thyroid extract in the belief that this acts synergistically with cortisone in helping to reduce pain from secondary deposits in bone from the breast. He thinks the dried thyroid may also help the process of recalcification and repair (Lemon and Reynolds, 1956).

The dosage of cortisone must be of the order of 100 mg. daily or, if it is given as prednisolone, 20-25 mg. a day. Lemon's regime is therefore gonadectomy (it is unnecessary to remove the ovaries in women over 70 years of age), methyl

testosterone by mouth, 30-80 mg. a day, or propyl testosterone, 50 mg. three times a week by injection, cortisone, 100 mg., or prednisolone, 20 mg. daily, and, in addition, 30-100 mg. of dried thyroid extract.

DEEP X-IRRADIATION

Irradiation of normal nervous tissue will not, in therapeutic dosage, either diminish or abolish painful nervous stimuli (Fleming, 1957). Central irradiation of the brain and spinal cord within safe limits for, for instance, cerebral and spinal-cord tumours, does not show any immediate effect upon the normal function of sensory or motor pathways. Heavy irradiation within the therapeutic range has, however, been known to cause, after a delay, gliosis in the brain and spinal cord, with clinical manifestations such as paraplegia. It is thought that this is due in large part to vascular ischaemia produced in the connective tissue rather than to direct action upon nerve cells and fibres. Relief of pain from radiotherapy is therefore, as in the case of cytotactic drugs, achieved usually by an indirect effect through its action on underlying diseased tissues.

This is illustrated in the treatment of carcinoma of the bronchus, where great symptomatic relief can be obtained in some carefully selected instances where pressure on surrounding structures has occurred. If, however, the tumour is apical, the so-called Pancoast tumour, irradiation, which necessarily involves the brachial plexus, will produce little or no relief of pain in the shoulder and arm.

Deep X-irradiation is of great value in controlling pain from some metastatic deposits in bone, particularly from the breast, or from invasion of bone by reticulo-sarcoma. It will control pain from such highly radio-sensitive abdominal tumours as lympho-sarcoma and seminoma. The successful eradication of many early growths by irradiation in such sites as the mouth and throat, skin, anus, vagina and bladder is often achieved with relief of accompanying painful symptoms. Headaches from both primary and secondary cerebral neoplasms may also be much relieved, a point worth remembering even when the outlook is hopeless.

Among the painful conditions in which radiotherapy may give symptomatic relief, mention must be made of Paget's disease of bone when the pain is reasonably localized, ankylosing spondylitis, acute subacromial bursitis and tendinitis, and the frozen-shoulder syndrome. An interesting example of the control of pain of inflammatory origin is provided by irradiation of the parotid gland in the early stages of acute parotitis. This may be of considerable practical importance if acute parotitis occurs when a patient is in a severely debilitated state.

ANALGESIC DRUGS

Concurrently or subsequently to the use of other methods, analgesic drugs will inevitably play some part in the treatment of chronic pain, and although we are still very largely dependent upon long-established analgesics there have been recently some advances in the manner in which they are used.

The value of mild analgesics is sometimes greater than is universally realized and is a point which has been supported on a more scientific basis by the interesting work of Beecher (1953), who showed that 10 gr. of acetylsalicylic acid was demonstrably more effective as an analgesic than 1/6 gr. of morphia or 1 gr. of codeine, all by mouth.

Beecher (1956) has also shown that placebos can have an effect on pain of undoubtedly organic origin, and that the significance to the patient of the lesion producing the pain can block or determine the pain experience.

The significance of a pain varies enormously, and it may even become so accustomed or protective that it is necessary to the patient, as Penman (1954) has shown in the case of trigeminal neuralgia.

The relief of anxiety by sensible discussion and possibly by the use of sedatives has long been a first step in the management of chronic pain. To this end chlorpromazine has been used in clinical practice for some time. There are many patients dying with malignant disease in whom resort to morphia can be delayed until the last hours of life, or even avoided altogether by its use. Chlorpromazine has no analgesic action of its own, but seems to potentiate that of narcotic drugs, as well as having its special effect of reducing the patient's emotional response.

It is the experience of most that large doses of chlorpromazine are required, and that the drug is far more potent by injection than by mouth. Gordon and Campbell (1956) gave it by mouth in 25 mg. doses four times in the day, with 50 mg. at night, thus making a total of approximately 150 mg. in 24 hours. They followed up, for a period of 1 to 18 months, 32 patients so treated who had intractable pain from carcinomatosis. They found no toxic effects from the drug beyond some drowsiness in elderly patients, and concluded that chlorpromazine is a useful adjuvant in the control of persistent pain. They observed an almost invariable reduction in the quantity of analgesic required. The mental outlook of their patients improved and, without exception, they ate and slept better when they were taking chlorpromazine.

When more powerful analgesia is required, i.e., in the control of pain from a coronary thrombosis, morphia or a substitute will be required. It is not proposed to discuss the numerous morphia substitutes which are now available, but merely to mention that methorphinan (Dromoran) is regarded by many experienced practitioners as particularly useful as it can be given effectively by mouth. It is also thought to be less habit-forming than morphia, and most women are less nauseated by Dromoran, pethidine (Demerol), or amidone hydrochloride (Physeptone), than by morphia. Nevertheless, all these drugs tend to produce some nausea unless the patient is more or less confined to bed.

The respiratory depression which is produced by morphine, pethidine and Dromoran can, it is claimed, be reduced by levallorphan tartrate in approximately 0·5-1·5 mg. doses but its effect on tolerance, addiction, nausea and constipation have not yet been fully worked out.

Another possible method of increasing the effectiveness of morphia and of diminishing its ill effects in the control of intractable pain in the terminal stages is its combination with amiphenazole (Daptazol), as described by Shaw and Shulman (1955). Further experience of this treatment in 127 patients has been reported by McKeogh and Shaw (1956). They found that even a very large dose of morphia, 55-160 mg. (grains 1-2½), when combined with 20 to 30 mg. of amiphenazole in the same syringe, was not followed by respiratory depression, narcosis or reduction in the cough reflex. They believe that, in addition, amiphenazole

retards the development of tolerance and has a caffeine-like effect, with a brightening of the patient's mental outlook. This method is clearly worthy of further trial, not only to permit large doses of morphia to be given when they are necessary, but also in the hope of making a smaller dose more effective than would have been possible without the addition of the Daptazol.

Apart from the use of combinations of newly synthesized drugs, numerous measures have been devised for the control of chronic pain, notably by neurologists. Such a method is the injection of the interspinous ligaments with local anaesthetic (Fischer-Williams, 1956). Anaesthetists also are interested in the control of intractable pain, and use their skill by injecting alcohol intrathecally or by blocking nerves. Surgeons have for many years done operations such as cordotomy and have more recently, in cooperation with psychiatrists, reduced the disadvantages and increased the advantages of leucotomy.

When all other measures have been exhausted and the nature of the situation is such that pain will persist until the patient's death, morphia or its substitute will often have to be given to the end. It is not, however, always necessary to resort to injections immediately and thus abandon the great advantages of oral medication. Whatever preparation or method of administration is chosen, it is sometimes wise to prescribe it at definite intervals throughout the day. The length of these intervals will be determined with the object of preventing the development of agonizing pain but not necessarily of abolishing pain entirely. If this is not done severe clouding of consciousness may alternate with periods of agony, or the patient may linger on interminably, to the distress of those who love him.

I feel we should try to avoid these things so that our patients may die with all possible dignity as well as in peace.

It is a pleasure to thank Mr. G. H. Bateman, Prof. J. B. Kinmonth and Dr. J. A. C. Fleming, all of St. Thomas's Hospital, London, for their kindness in allowing me to refer to their work.

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THE SURGICAL PATHOLOGY OF BILHARZIASIS*

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This continent of Africa is not only heir to those diseases common to man throughout the world, but serves as the repository of special parasitic diseases widespread throughout this vast land. Of these none is so prevalent, so refractory to prophylactic control and so insidious in its clinical progress as bilharziasis. It has been estimated that over 100 million human beings in Africa suffer from schistosomiasis, and if regard be given to its general and visceral effects it becomes clear that this disease provides the greatest challenge to preventive medical endeavour on this continent.

The schistosomal trio clinically important to man are *S. haematobium*, whose main habitat is in the urinary system, *S. mansoni*, which has a special predilection for the digestive system, and *S. japonicum*, which exists, with its intermediate snail-host the *Oncomelania nasophora*, in Japan, China and the Phillipines. The fresh-water snail is the essential intermediate host in the life-cycle of the schistosoma; the species *Physopsis africana* of the genus Bullinus being the main intermediate host for *S. haematobium*, whilst the *Biomphalaria pfeifferei* of the genus Planorbis is similarly the intermediate host for *S. mansoni*.

S. haematobium is rarely found outside the African continent, whilst *S. mansoni* exists not only in Egypt, East and West Africa and Madagascar alongside haematobium, but as the sole form of schistosomal infection in South America and the West Indies. Bilharzial infestation in Africa occurs in a wide belt, extending along the Nile into the Sudan, along the East coast including Eritrea and Somaliland into Uganda, Tanganyika and Kenya and spreading centrally into the Belgian Congo. The Central African Federation of the Rhodesias and Nyasaland is heavily infested, and the establishment of vast water conservation schemes and irrigation networks and its rapid industrialization will undoubtedly increase its incidence for, despite measures aimed at killing the snails in the water courses of the affected areas and early diagnosis and treatment of human victims, it is unlikely that this disease will be contained until a natural biological antagonist to the snail is found and developed. Mozambique and the Eastern half of South Africa (Transvaal and Natal) also suffer bilharzial infestation, the belt extending to the Cape. Similarly affected are portions of Nigeria, Ghana, French West Africa, Algeria, Morocco and the Middle East.

The sexually distinct, digenetic trematodes of the schistosoma family inhabit the portal system of the human victim of the disease. The 11-mm.-long male worm is shorter and broader than the female of the species and widens just caudally to its ventral suckers to form a gynaecophoric canal, within which the female is enclosed in times of sexual activity. The conjoined couple travel against the course of the portal blood stream, the terminal-spined ova of *S. haematobium* reaching the vesical plexus to be deposited in bladder

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and lower ureter, whilst the lateral-spined ova of *S. mansoni* are deposited mainly in the colon and rectum.

Many eggs are voided in the urine or faeces, and perpetuation of the life cycle becomes contingent upon their reaching the intermediate host within 24 hours. With disintegration of the chitinous shell of the ovum, its contained miracidium is released to penetrate into a snail, where it develops through the sporocyst stage into the bifid-tailed larval cercariae. The cercariae leave the snail and coming into contact with the skin or mucous membrane of man, pierce the lymphatics to reach the venous system and are thence distributed to their ultimate visceral locale.

During this 4-6 week period of migration, systemic disturbances often referred to as the Katayama syndrome are common. General ill-health, malaise and proneness to fatigue may be complained of, whilst recurrent bouts of pyrexia, urticaria, transient pulmonary infiltrations, lymphadenopathy and enlargement of liver and spleen may be manifest. Haematological examination may disclose a normochromic or hypochromic anaemia associated with an eosinophilia of the order 10-60%. At this stage a positive cercarial skin test and a positive complement fixation test may elucidate the clinical problem and permit of early commencement of a curative course of systemic antimony therapy.

THE VISCERAL LESION

I should like here to consider the irreversible effects of visceral bilharziasis and the surgical implications involved. It is as well to appreciate that apparent cure of schistosomal infestation with the trivalent antimony preparations is no guarantee that the patient who has suffered visceral ovideposition will not present, months or years later, with effects of luminal distortion or obliteration.

Ovideposition initiates a constant pathological pattern, details and variations depending upon the intensity and duration of the infection. Though ova are generally deposited in the submucous and subserous layers, no visceral layer is immune from its effects. The ova initiate an inflammatory foreign-body reaction, resulting in intense engorgement of the surrounding capillaries and causing local oedema and hyperaemia. The cellular response is not long delayed and focal aggregations of lymphocytes, monocytes and eosinophils collect round each ovum. Though the arrangement of the cells is irregular at first, they soon form a concentric ring round the ovum with the eosinophils retaining prominence. The hyperaemia gradually resolves, the capillaries undergoing endarteritic changes. Central necrosis follows, the ova becoming unrecognizable or undergoing hyalinization and calcification. Large multinucleated giant cells make their appearance, their nuclei having an irregular distribution throughout the cellular protoplasm. This basic cellular reaction results in the formation of bilharzial tubercles due to conglomeration of these microscopic complexes. Fibrosis and calcification of these localized tubercles provide the 'sandy patch' appearance so pathognomonic of the visceral lesion. Coalescence of many tubercles gives rise to a large avascular mass, comparable to the gumma of syphilis or the tuberculoma of Koch's bacillus, so that this bilharzial granuloma may well be referred to as a bilharzioma.

The tendency for mucous membranes to form projections in response to irritation is well known, and this tendency is well exemplified in the papillary formations which develop in the urinary and alimentary tracts in response to continued irritation by bilharzial ova. These papillary projections may bleed or ulcerate, ulceration sometimes extending to produce sinuses and fistulae.

The round-cell infiltration earlier described is soon followed by the appearance of fibroblasts, which lay down a fine fibrous reticulum that rapidly matures and, involving all the coats of the affected viscus, may cause partial or total obliteration of its lumen. Deposition of calcium, though variable in degree, may be a very prominent feature.

THE URINARY SYSTEM

The Bladder

The urinary tract is peculiarly susceptible to ovideposition by *S. haematobium*. The vesical irritant sets up a local inflammatory reaction which may be visualized early in the disease, at a stage when microscopic examination of the urine will show it to be teeming with terminal-spined ova and red cells, cystoscopic examination of the bladder then disclosing an intense hyperaemia and oedema of the periureteric vesical mucosa. In the course of the subsequent 6 weeks greyish tubercles become discernible on the trigone of the bladder and around the ureteric orifices, a fine zone of hyperaemia often still persisting round some of the tubercles. Urinary microscopy, at this stage, often fails to disclose ova, though leucocytes and pus cells may be present. Cystoscopic biopsy of a tubercle will permit histological confirmation of the diagnosis. Though haematuria, dysuria or the effects of superposed cystitis may be the presenting features, prolonged lassitude, backache or a persistent eosinophilia may often be the only clinical indication of bilharzial infestation, cystoscopy being necessary to demonstrate the presence of vesical ovideposition. Blockage of the vesical submucous glands consequent upon the inflammatory reaction results in the formation of pale bullous cysts, which are seen at cystoscopy to be arranged focally or in clusters. Occasionally the appearance is that of cystitis cystica.

Cystoscopic control during systemic antimony therapy permits assessment of the degree of local response and assurance that the lesions are reversible. After completion of treatment the affected vesical mucosa bears a permanent golden-yellow punctate appearance due to the deposition of cholesterol esters in the healed and fibrosed follicles.

With progression of the bilharzial cystitis, the vesical epithelium becomes heaped up into papillary projections by the vascular granulation tissue which develops. It is, I believe, wrong to refer to these papillary masses as papillomata, for these masses are neither neoplastic nor do they have the malignant propensities of true papillomata. They respond extremely well to a combination of systemic therapy and local fulguration, so that the term papillary bilharzioma adequately defines the inflammatory nature of the lesion.

Ulceration of the bladder, although not usually a prominent feature, may extend widely and deeply to penetrate adjacent structures. As malignant vesical ulceration may co-exist with bilharzial cystitis, it is wise to perform histological study of a biopsy of the ulcer before commencing systemic treatment. Massive vesical ovideposition may result in a chronic interstitial cystitis, producing a small contracted bladder and corresponding back pressure effects.

Vesical and, occasionally, ureteric calcification follow heavy local infestation. The calcification is mainly confined

to the submucous and muscular layers and, being arranged concentrically, provides a radiological similarity to a foetal head *in utero*. Phosphatic incrustation of the bladder mucosa may occur as a result of secondary infection with urea-splitting organisms.

If one takes into consideration the fact that bilharziasis in the Salisbury region affects 10% of the European population and 80% of the Bantu community, and if cognisance is taken of the fact that the African presents with far-advanced pathological sequelae in his urinary tract, it would be anticipated that urinary calculi would occur frequently in the African. Yet amongst 66,842 consecutive African hospital admissions between March 1949 and March 1955, there were only 14 cases with urinary calculi, an incidence of 0·02%. Amongst 28,547 consecutive European hospital admissions during this same period there were 84 cases with urinary calculi, an incidence of 0·28%. It may be recalled that when McCarrison investigated the cause of the high incidence of urinary calculi in Southern India, he demonstrated that a high dietary calcium and low vitamin-A content were the most important aetiological factors. It is, therefore, interesting to find that an analysis by Fox of the African dietary showed it to be low in calcium content and variable in vitamin-A content, and to provide an acid ash residue.

It is, accordingly, not illogical to infer that urinary stagnation and sepsis is less important in the pathogenesis of urinary calculi than maintenance of an acid pH in the urine and a low calcium excretion.

There has been much difference of opinion regarding the aetiological relationship between bilharzial infestation and carcinogenesis and my own view is that bilharzial ova do not exert a focal carcinogenic effect, despite the fact that chronic bilharzial cystitis and vesical carcinoma not infrequently co-exist. If bilharzial ova could exert a focal carcinogenic effect it would surely exert this effect in other organs where ovideposition is common. Similarly it might be anticipated that vesical carcinoma due to bilharzial irritation would be a squamous-cell type, yet the usual pattern of carcinoma, in the cases I have studied, has been of an anaplastic cellular type. I have also observed that the maximal cellular proliferation and anaplasia often occurs where ova are absent or exist in minimal concentration, so that the impression is obtained that the fibrosis induced by the ova keeps at bay the cellular advance. Recent studies of tryptophane metabolism has suggested that excretion of unconjugated hydroxy-anthranilic acid in the urine may initiate vesical malignancy and similar studies in patients with chronic vesical bilharziasis may serve a useful purpose.

The Ureter

Ovideposition in the lower ureter is followed by an inflammatory response which, as elsewhere, is characterized by early infiltration by monocytes, lymphocytes and eosinophils. The cellular infiltration and vascular granulation tissue which develops causes a disintegration of the muscle layers, with vacuolation and hyalinization of the muscle fibres. Fibroblastic activity follows and the ensuing ureteric ulceration and fibrosis leads to varying degrees of cicatrization, stricture and obliteration of the affected portion of the ureteric lumen. Back pressure, and secondary infection produces varying degrees of hydronephrosis, pyonephrosis or ascending pyelonephritis.

I have indicated above that the earliest vesical involvement occurs in the periureteric region, and it may accordingly be anticipated that cicatrization and fibrosis at the ureteric orifice would result in stricture or obliteration of that orifice. This not infrequently occurs, but occasionally the traction effects of peri-ureteric fibrosis results in the production of a gaping 'golf-hole' ureteric orifice not unlike that seen in tuberculosis. Such an orifice may exist unilaterally or bilaterally, or may be associated with stenosis of the contralateral side. The resultant incompetence of the uretero-vesical mechanism will permit reflux of urine up the ureter and augmented by superposed sepsis gives rise, in progressive manner, to one form of bilharzial mega-ureter and hydronephrosis.

Intrinsic ureteric lesions are generally confined to the lower one-third of the ureter, though concomitant strictures may exist more proximally, and the degree of pathological change will determine whether ureteric stricture or ureterectasia will occur. By ureterectasia I mean a primary focal dilatation in the lower ureter, unassociated with distal obstruction or uretero-vesical incompetence. It is a lesion which is caused by the constant stress imposed by the propulsion of urine on an area weakened by fibrous-tissue replacement of the destroyed contractile muscle layer. This localized dilatation results in varying degrees of neuromuscular incoordination in the ureteric propulsive effort, and progressive dilatation occurs in a cephalad direction. Whether ureteric stricture or ureterectasia will develop in a case of bilharzial ureteritis depends on the degree of destruction of the muscle layer and the quality and quantity of the fibroblastic reaction.

Bilharzial mega-ureter and hydronephrosis may thus follow ureteric stricture confined to the orifice or to the pelvic ureter; it may be a sequel of ureterectasia or of ureteric calcification; it may result from uretero-vesical incompetence, or it may be caused by back pressure from a small-capacity bladder.

Assessment of the extent of structural and functional disturbance in the urinary system naturally requires a comprehensive investigation. Urinalysis will disclose the presence or absence of active bilharzial infection, as well as the nature and drug sensitivity of any secondary infecting agents. Cystoscopy is necessary to assess the extent of vesical involvement and to gauge the degree of ureteric implication, appropriate instrumentation being carried out at this time. Biopsy of any suspicious area is performed, whilst the intravenous injection of 0·4% indigo carmine permits an immediate assessment of renal function.

Radiological examination is never omitted, straight X-ray of the abdomen and intravenous and retrograde pyelography demonstrating the architectural pattern of the diseased urinary tract. Cystography permits evaluation of the degree of uretero-vesical incompetence and reveals the presence of ureteric reflux.

Estimation of the blood non-protein nitrogen and blood urea provide a satisfactory guide to the functional efficiency of the kidneys.

The aim of surgical treatment is to provide the greatest degree of relief from the irreversible effects of urinary bilharziasis. Naturally, active bilharzial infection must receive an effective course of antimony therapy before any operative manoeuvres are commenced, whilst appropriate control of secondary urinary infection will often prevent or hold in check progressive structural changes.

Cystoscopic meatotomy of the stenosed or cicatrized ureteric orifice, followed by regular bougie dilatation, may confer great benefit on the patient, whilst ureteric bouginage often controls stricture of the lower ureter and prevents back-pressure effects. Bouginage, however, is useless in ureterectasia, so that an early decision should be made to resect this segment of ureter if recurrent sepsis or back-pressure effects ensue. Similarly, ureteric resection is carried out if a stricture is impassable or repeated dilatations prove ineffectual. After resection of several inches of lower ureter I have always found it possible to perform a uretero-cysto-neostomy, but should excessive tension prevent anastomosis it is well to be prepared to bridge the gap with a length of ileum. Transplantation of the ureters into the pelvic colon would be indicated if a completely disorganized bladder with internal or external fistulae existed, whilst ileocystoplasty may permit an increase in bladder capacity where this is desirable. Nephrectomy or nephro-ureterectomy may have to be performed on its merits, but one must be absolutely certain that the contralateral kidney is not affected by progressive disease. Nephrostomy or pyelostomy may be a necessary preliminary manoeuvre to improve the function of the kidney on that side before excision of the strictured distal ureter can be considered.

THE ALIMENTARY SYSTEM

Bilharzial Appendicitis

The appendix is one of the organs that frequently suffers the deposition of bilharzial ova. It is interesting to note that in 92% of appendiceal bilharziasis, the *S. haematobium* is the infecting agent and this, no doubt, explains the not infrequent association of a mixed urinary and appendicular clinical pattern. From clinical, operative and pathological assessment of this condition it has become clear that the relationship between the appendix and bilharzial infection may take 2 forms:

1. Appendiceal bilharziasis. Ovideposition occurs in the appendix, as it may also in the gall-bladder, pancreas or other viscera, and undergoes the natural healing process without involvement of the lumen or the development of a granuloma.

2. Bilharzial Appendicitis. This is a true clinico-pathological entity which results from partial or total obliteration of the lumen. The obstructive effect of partial obliteration of the lumen not infrequently predisposes to the complication of acute pyogenic appendicitis with abscess formation, gangrene, perforation and peritonitis.

Ovideposition results in the customary cellular response; at laparotomy tubercles are visible to the naked eye on the serosal aspect of the appendix and may also be seen in the meso-appendix, on the caecum, and on adjacent viscera, viz. bladder, uterus, tubes and ovaries. Extension and conglomeration of submucous lesions leads to the destruction of lymphoid follicles and their replacement by fibrous tissue, with distortion, narrowing or obliteration of the lumen. Ulceration of the mucosa is often in evidence, while superposed pyogenic infection, acute or subacute, may occur distal to the luminal distortion.

Progression of the fibro-cellular reaction in the serous and subserous coats may result in the formation of a large granulomatous mass attached to the appendix, or the appendix may be incorporated in the granulomatous process, resulting in a mass 3-4 cm. in diameter.

The pathological technique in the demonstration of visceral schistosomiasis requires some mention. Examination of the appropriate tissue or organ will, in a high proportion of cases, demonstrate not only the characteristic fibro-cellular reaction to the ova, but will also permit recognition of hyalinized, fibrosed or calcified degenerate ova. To permit recognition of ova in all cases, however, it is necessary to digest the organ in 10% caustic potash at 60°C for 10 hours before examining the residue for ova.

There is little need to recount the well-known clinical features of chronic appendicitis. Suffice it to state that the patient may present with chronic appendicular dyspepsia, with persistent pain in the right iliac fossa, or with the features of acute appendicitis. Special mention, however, needs to be made of the not infrequent association of diarrhoea and the occasional manifestation of melaena with the appendicular syndrome, for these features may cause diagnostic difficulties. Other causes of these latter symptoms must, of course, be excluded. Appendicectomy performed for the relief of appendicular dysfunction in these cases also cures the episodic bouts of diarrhoea and melaena, pathological examination demonstrating the bilharzial involvement of the appendix.

Bilharzial Colitis and Proctitis

S. mansoni has a great predilection for the part of the alimentary system that is drained by the inferior mesenteric vein. The earliest changes visualized sigmoidoscopically are those of a congested haemorrhagic mucosa which bleeds rather readily. Shallow rounded or oval ulcers surrounded by normal intervening mucosa may be seen and biopsy of these areas invariably permits identification of the causative ova, even on occasions when stool examinations are negative. Bilharzial colitis or proctitis is a potent source of diarrhoea, which may be very severe, with pus and blood in the stools, if ulceration of the bowel is very extensive. Proliferative fibro-cellular changes may give rise to pseudo-polypi not unlike those seen in ulcerative colitis, but there are no indications that these lesions are premalignant. A bilharzial granuloma of the rectum may attain a large size, making its clinical differentiation from carcinoma almost impossible. Histological examination of a biopsy specimen with demonstration of ova, and the therapeutic response to systemic therapy naturally solves the diagnostic problem. Similarly the presence of ulcerative or proliferative peri-anal or perineal lesions, occurring in people coming from bilharzia-infested countries, should suggest a bilharzial origin.

Genital Bilharziasis

Though minor evidence of ovideposition is often encountered in the tubes, ovaries and broad ligaments, occasionally frank pathological sequelae may develop in vulva, vagina, cervix or tubes. Chronic bilharzial salpingitis may present as a paratubal granuloma or tubo-ovarian mass which is clinically palpable, or it may cause symptoms because of partial or total obliteration of a tubal lumen. Submucous ovideposition may lead to a progressive disorganization of the mucosal, muscular and serosal layers with narrowing or obliteration of one or both lumina. Naturally, sterility results when both tubes are completely obliterated, but partial obliteration of a tube by bilharzial fibrosis may predispose to ectopic gestation. Bilharzial involvement of the vagina and cervix not infrequently occurs in the African, the present-

ing leucorrhoea reflecting either an area of hyperaemia, an ulcer, or a papillary bilharzioma. A proliferative lesion of the cervix may very readily be mistaken for carcinoma. Lesions of the vulva may manifest themselves either as an exuberant granuloma or as an area of ulceration involving the vestibule or clitoris. Diagnosis naturally depends on the finding of ova in the scrapings or section.

It is a well-known fact that one of the earliest clinical manifestations of urinary tuberculosis in the male is a tuberculous epididymitis. In great contrast to this, however, is the relative rarity of male genital bilharziasis. Nevertheless, bilharzial disease of testicle, cord, prostate, seminal vesicles and urethra do occasionally occur, and the possibility of such lesions should always be kept in mind.

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CUTANEOUS NERVES IN HERPES ZOSTER

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The object of this investigation is to ascertain whether any changes can be found in the nerve fibres of the cutis and subcutis in cases of herpes zoster. Von Baerensprung [1] was the first to draw attention to the fact that herpes zoster is essentially a nerve disease. No attempt was made to prove this by means of pathological investigation until the classical researches of Head and Campbell,[2] published in 1900. They dissected the posterior root ganglia in cases suffering from herpes zoster who died of a concurrent or subsequent disease, and found haemorrhage and destruction of the ganglion cells. By means of the Marchi method they also demonstrated degeneration of the posterior root fibres. They traced the degeneration of the peripheral nerves as far as the skin but then had to admit that they had 'not succeeded in demonstrating degenerate fibres in the actual portion of the skin examined'.

Many papers on the pathology of herpes zoster have been published since this report first appeared. All have stressed the destruction of ganglion cells in the posterior root ganglia. Ramsay Hunt[3] demonstrated the same degeneration in the cells of the geniculate ganglion in cases of otic zoster. He used the findings to map out the cutaneous distribution of the sensory branch of the facial nerve. In 1949 Ebert[4] published an article in which he claimed to have shown degeneration in the intracutaneous nerve fibres by using the Gay Prieto modification of Cajal's silver method.[5] He found definite signs of degeneration in the nerves 13 days after the commencement of the disease. The criteria used by Ebert to decide whether actual nerve degeneration was present can in some instances be criticized. He maintains that 'some nerve bundles in the middle and deeper parts of the corium were found to have *much less than the normal* number of fibres' (my italics). The number of fibres in various nerve bundles in the skin varies widely, and even in normal skin I have found that counting the fibres in different parts of one bundle, as it runs through the corium without apparent branching, will give very different figures. One must therefore question Ebert's statement about the 'normal number of fibres'.

Material

Biopsies were performed on 10 cases of herpes zoster, at times varying from 5 to 68 days from the onset of the disease. In one case, a 60-year-old European, with herpes zoster of Th10, a biopsy was taken 15 days after the onset and another 68 days after the onset. In a few instances the biopsies were done by means of an electric punch without local anaesthetic, because it was feared that the procaine might interfere with the impregnation of the nerves. The majority, however, were done with a scalpel under local procaine anaesthetic. The full thickness of the cutis and subcutis down to the subcutaneous fat was removed.

Controls

Biopsies were performed on two cases of varicella 3 days after the onset of the disease, and on 1 case of herpes simplex. A considerable amount of normal material was accumulated, mainly from wide biopsies done for the removal of warts and naevi.

Technique

A modified Gros-Schultze[6] method was used, as follows: Fix for a minimum of 14 days in 10% formol containing 8 minims of added pyridine puris in every 100 c.c. Cut frozen sections at 45μ and wash sections for 1½ minutes in 2 changes of distilled water. Impregnate for 2 hours in 20% silver nitrate solution and transfer directly to 5 or 6 consecutive Petri dishes containing 1 : 4 formol at pH 6·8 for a total of about 20 minutes or until no more white sediment is discernible. Differentiate in a solution of silver nitrate and ammonia and wash in several changes of distilled water. Gild, dehydrate, and mount in Canada balsam.

With this technique the nerve fibres are stained black or purple and the co-staining of all mesodermal tissue can be kept to a minimum. The epi- and perineurium stains very faintly and no differentiation can be made between medullated and non-medullated fibres. Owing to the necessity of using frozen sections, serial following of any particular nerve is impossible.

The Marchi[7] method was found to be impractical for skin material as it was impossible to prevent excessive co-staining of collagen fibres.

With the Gros-Schultze method normal skin shows 2 different types of nerve fibre, usually found together in small nerve bundles:

(*a*) Coarse fibres, often showing distinct beading, and resembling a rosary. (Fig. 1). In the past this beading has often been mistaken for a sign of degeneration. The number

of these fibres varies considerably in nerves of apparently the same size.

(*b*) Fine fibres, usually of about half the diameter of the above, seldom showing beading. These fibres are definitely in the majority in normal cutaneous tissue, the ratio of fine to coarse fibres never being less than 6 : 1.

In addition to bundles of nerve fibres running together enclosed in a sheath, there are also numerous loose, single fibres running criss-cross through the corium. (An incidental finding during this investigation was the fact that in the vaginal wall almost all these fibres run at right angles to the long axis of the vagina.)

In one biopsy taken from a recently bruised area of otherwise normal skin, no sign of degeneration of nerve fibres could be found in spite of considerable extravasation of blood etc., which was demonstrable with haematoxylin-and-eosin staining. This is of interest in the light of Klauder's views[8] on the traumatic aetiology of herpes zoster.

The sections of the two cases of varicella showed no deviation from the normal as set out above, though admittedly the biopsies were taken before the end of the 7-day period which was found to be the minimum time in which nerve degeneration appears. Repeat biopsies were unfortunately not possible in these cases. Sections of the biopsy of a herpes-simplex lesion also showed no sign of nerve degeneration. Here again the biopsy was taken before the 7th day, for obvious reasons. With the Gros-Schultze technique it was found in apparently normal skin that in some instances only one or two fibres became impregnated in quite large bundles. The reason for this is unknown. Such nerves create the impression of degeneration on superficial examination. It was therefore decided that only a ratio difference or total disappearance (see below) could be accepted as evidence of pathological change.

FINDINGS IN HERPES ZOSTER

In no sections of herpes zoster biopsies made before the 7th day of the disease was any sign of nerve pathology seen. This differs from Ebert's findings, where degeneration was only demonstrated after the 13th day. In all the remaining sections, including those of the biopsy taken 68 days after commencement of the symptoms, the following was found on examination of the nerve bundles:

Most bundles, especially those immediately underneath the bullae or scars, showed complete absence of all fine fibres, but no difference was discernible in the coarse fibres (Fig. 2). The nerves immediately adjacent to the lesion often had no fine fibres but sometimes only one or two were found in a large bundle containing 15 or more coarse fibres (Fig. 3). Up to 2 mm. from the actual lesion 30% of the nerves showed either total absence of fine fibres or a great reduction in their numbers so that the ratio of coarse to fine fibres was never less than 3 : 1. All nerves more than 2 mm. removed from the lesion were apparently normal.

Underneath the lesion no loose, single fibres were found in any section examined, with the exception, of course, of the biopsies taken before the 7th day of the disease (see above). These loose fibres were again present almost immediately adjacent to the actual site of the lesion.

CONCLUSIONS

The only difference demonstrable with this technique between nerves in normal skin and those in cases of herpes zoster

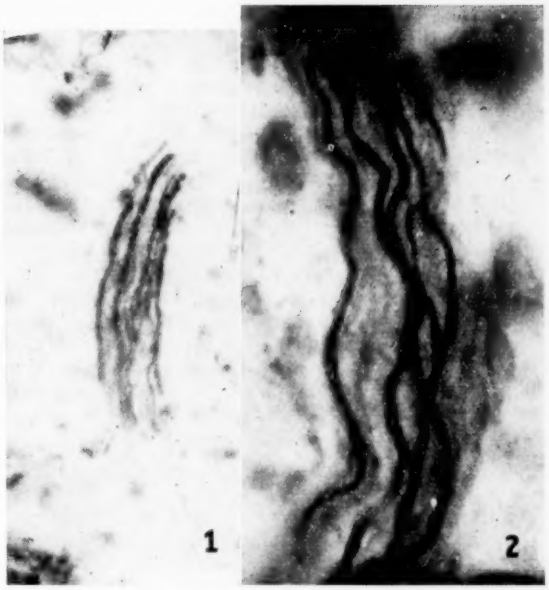

Fig. 1. Normal skin from Th9, European male. Four coarse fibres can be seen showing beading. The fine fibres are less clear because they are on a slightly different optic plane.

Fig. 2. Nerve directly under a scar in a case of herpes zoster. The biopsy was made 17 days from the onset of the disease. Five coarse fibres can be seen. Only one fine fibre is visible giving a ratio coarse to fine fibres 5 : 1.

Fig. 3. Skin from patient with herpes zoster of C.6. Biopsy done 13 days after onset of the disease. The nerve is just beyond the 2 mm. radius from the scab. Numerous fine fibres can be seen though not distinctly. High magnification to show marked beading.)

was the absence or reduction of the fine fibres in the bundles and the absence of loose running fibres. In no case was an actual degenerating fibre seen. The coarse fibres showed no apparent deviation from the normal. Counting the fine fibres is regarded as being more reliable than counting all the fibres as done by Ebert; it is the relative absence of fine fibres which is considered to be of significance.

SUMMARY

The cutaneous nerves in 10 cases of herpes zoster were examined by means of the Gros-Schultze method of silver impregnation. It was found that after the 7th day from the onset of the disease the fine fibres, which are normally more numerous than the coarse fibres, are either totally absent or greatly reduced in number. The nerves more than 2 mm. removed from the actual vesicle or its scar were completely normal. Control biopsies made on varicella and herpes-simplex cases showed normal nerves throughout.

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A NEW SYNDROME FOR THE EARLY DIAGNOSIS OF ULCERS SITUATED HIGH ON THE LESSER CURVATURE OF THE STOMACH

A. SHEDROW, M.D., M.R.C.S., L.R.C.P.

Johannesburg

In a preliminary communication[1] I drew attention to a symptom-group for diagnosing high-situated ulcers on the lesser curvature and submitted records of 4 cases. Since its publication I have seen a further case of a gastric ulcer which fits into the new clinical picture.

I propose therefore to formulate this syndrome in the following clinical picture:

1. *Chest pain*, situated in the infra-clavicular region, mostly on the left side, but occasionally on both sides. The pain is cramp-like and sometimes constricting, and becomes worse after remaining long in the sitting position.

2. *Pain in the back*, situated at the lower part of the left scapula and below it. It appears either in conjunction with the chest pain, or at other times.

3. *Absence of the epigastric pain*, which is observed in most cases of gastric ulcer.

4. *Absence of other gastro-intestinal symptoms.*

From this picture one should be able clinically to diagnose a high-situated gastric ulcer of the lesser curvature. In the past I have found the above-mentioned symptoms misleading; they were interpreted as caused by intercostal neuralgia, fibrositis, vague chest conditions etc. When ordinary therapy failed, an X-ray examination would reveal nothing in the chest and an electrocardiogram would also show nothing abnormal. It was only after prolonged and time-wasting examinations, and often after a sudden and unexpected episode such as haematemesis, that the diagnosis would be made. Most of the patients thought that they had an ordinary cold and used embrocations and aspirins, by which their pain was temporarily eased.

It is important that the clinician should be on guard against being misled by chest pain unaccompanied with other symptoms of gastric pathology. The infrequency with which a clinical diagnosis of gastric ulcer of the lesser curvature is made, compared with that of duodenal ulcers, suggests that the clinician is either missing this syndrome, or is misinterpreting it.

The additional case referred to above is as follows:

A patient, male, 46 years of age, with no previous history of any gastro-intestinal disturbances, came to consult me for pain in the chest and in the back, which began 2 months previously. This pain was aggravated after prolonged sitting at his desk at work. He took aspirin, which temporarily eased the pain. The pain had no relation to food intake, he had no hunger pain, no heartburn, no vomiting and no haematemesis, and his appetite was good. A few weeks after these symptoms began he had felt pain in the left hypochondriac region and occasional epigastric discomfort but, in his own words, what worried him most was the chest pain. On examination, the pain was found to be localized high up in the chest, in the region below the left clavicle, and in the back at the lower part of the left scapula and below it. Epigastric pain was not then present, and there were no other gastro-intestinal symptoms. There was no evidence of any cardio-vascular condition, and nothing was found on examination of the chest.

Diagnosis. In view of the symptoms found on this patient, I diagnosed a gastric ulcer of the lesser curvature. The patient was X-rayed the next day by Dr. Eric Samuel, and the diagnosis was confirmed (*Fig.* 1) by the finding of a large ulcer of the lesser curvature together with a shallow duodenal ulcer. I regarded the chest pain and the absence of gastro-intestinal symptoms as characteristic of ulcer of the lesser curvature and the pain in the left hypochondrium and the epigastric discomfort (very moderate as they were) as caused by the duodenal ulcer.

Fig. 1.

DISCUSSION

I have been unable to find any reference to this syndrome in the medical literature.

Epigastric pain is considered as the most important symptom in gastric ulcer. According to Bockus,[2] it is present in 75% of cases of that condition. Pain in the upper left quadrant of the epigastrium (left hypochondrium) may be a sign of ulcer of the lesser curvature near the cardia (Hurst, quoted by Bockus). In gastric ulcer, a less frequent sign than epigastric pain, Bockus observes, is pain localized behind the sternum between the substernal notch and the xyphoid cartilage. Boas (quoted by Bockus) is credited with the first description of circumscribed areas of tenderness in the back in patients with peptic ulcers; he located them at the right or the left of the spinous processes of the 10th, 11th and 12th thoracic vertebrae (Bockus). Bockus found that pain in the back was higher, between the 8th and the 10th thoracic vertebrae.

In all these cases where pain was localized in the chest (sub-sternal region), in the back and in the epigastrium, other gastro-intestinal symptoms accompanied that pain.

Pain will also vary according to the site of the ulcer; ulcers located near the cardia, at the bulbo-pyloric junction, or in the pyloric segment, will cause more pain than ulcers in the body of the stomach or on the lesser curvature, because of the increased muscle tonicity. Ulcers thus situated account for (1) visceral pain and (2) referred pain. Ulcers situated on the lesser curvature, especially those high on the curvature, present only referred pain, and no visceral factor is involved in the causation of that pain. This affords an explanation of the absence of orthodox gastric-ulcer symptoms in ulcers of the lesser curvature.

Ulcers of the lesser curvature, especially nearer the cardia, are infrequent compared with other parts of the stomach. The topographic distribution of 196 gastric ulcers in autopsies at the Cook County Hospital is as follows:[3] 59% are located in an area near the pyloris extending from the sulcus angularis for a distance of 3 inches cephalad; 7% around the cardiac area; 7% on the greater curvature, mostly near the cardiac zone (2% in the body of the stomach); and 25% on the lesser curvature. More ulcers were found in the lower part of the lesser curvature than in the upper part.

Radiologically it is sometimes difficult to diagnose an ulcer situated high on the lesser curvature and vague irregularities of the lesser curvature may present problems for interpretation. When chest pain exists and a gastric ulcer is suspected, X-ray examinations should be repeated until reliable information is obtained. If, in spite of all efforts, radiological tests remain negative, and symptoms persist, exploratory intervention is essential. It must be borne in mind that ulcers of the lesser curvature, especially those that are high situated, are prone to undergo malignant degeneration.

Resuming the question of pain in gastric ulcers, we find that a majority present epigastric pain, that sometimes referred pain is observed in the back, and that at other times chest pain (substernal) is noticed. The syndrome which I have described differs from this not only by reason of the absence of gastro-intestinal symptoms but also in the different localization of the pain (which is a referred form and not visceral pain). The chest pain described by other authors was low and sub-sternal, invariably suggesting coronary disease, and the pain in the back was also low. In our cases, both the chest pain and pain in the back were much higher.

Unless the practitioner is aware of the significance of the clinical picture I have described, his mind is likely to be deflected from the ulcer, which is the real source of trouble, until a subsequent incident occurs, such as haematemesis or signs of malignancy

CONCLUSIONS

1. A syndrome is described enabling the clinician to make an early diagnosis of high-situated ulcers of the lesser curvature of the stomach. An illustrative case is described, supplementary to those described in an earlier article.[1]

2. The difficulties which the clinician encounters when dealing with this clinical picture are described.

3. Attention is drawn to chest pain, its localization, and its differentiation from other types of chest pain. Special attention is drawn to the pain in the back, which is higher than that described by other authors in cases of gastric ulcer.

4. A cardinal point I stress is the absence of gastro-intestinal symptoms.

5. I also stress the importance of repeated X-ray examinations (which may sometimes present difficulties in interpretation) when dealing with high situated ulcers of the lesser curvature of the stomach. Surgical intervention is necessary when radiology fails to give definite information and the symptoms persist, in order to forestall malignant degeneration of the ulcers.

6. Pain in this syndrome is referred pain and not visceral. This is in contrast with ulcers in other parts of the stomach.

7. It is important that practitioners should be aware of this syndrome and its significance. It is suggested that lack of this knowledge accounts for the low incidence of recorded cases of ulcers of the lesser curvature of the stomach.

I wish to thank Dr. Eric Samuel for the X-ray reproduction.

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RESEARCH FORUM

CHLOROTHIAZIDE—A NEW DIURETIC : SOME OBSERVATIONS ON ITS ACTIONS AND USES

S. J. SAUNDERS, M.B., CH.B., AND L. EALES, M.D., M.R.C.P.

At a meeting of the Research Forum of the University of Cape Town held at Groote Schuur Hospital, Cape Town, on 11 December 1957, a paper was read by Dr. S. J. Saunders and Prof. L. Eales from the C.S.I.R. Clinical Nutrition Research Unit, Department of Medicine, University of Cape Town, and the Groote Schuur Hospital, of which the following is an abstract:

Experience with chlorothiazide, a new oral diuretic, was reported.

Detailed clearance studies showed chlorothiazide to be an effective naturetic and chloruretic agent acting by depression of tubular reabsorption. Potassium loss was variable. There was some increase in the urinary bicarbonate. This latter finding might be interpreted as evidence of associated carbonic anhydrase inhibition, the degree of which was surprisingly small considering the chemical structure of chlorothiazide, and its known activity as a potent carbonic-anhydrase inhibitor *in vitro*.

In one patient there was a transient rise in the glomerular filtration rate.

The administration of 500 mg. of chlorothiazide to 3 normal subjects on a sodium-restricted diet resulted in a loss of sodium, potassium and chloride in the urine. Definite hyponatraemia ensued. This was associated with considerable lethargy and headache in 2 of the subjects. This study is still in progress.

Clinical experience in 22 patients with oedema was reported. Cardiac oedema was present in 14, and in these the response to the drug was good in 10, fair in 2, poor in 1, and absent in 1. There were 6 patients with nephrotic oedema, and 4 of these responded well to the chlorothiazide while 2 did not respond. Two other patients, one with liver disease and another with constrictive pericarditis and liver disease responded well. In several of these, detailed studies of electrolyte excretion were made. It is possible for patients previously resistant to mersalyl to respond to chlorothiazide, and also for the reverse to occur. Adequate response is usually obtained with a dose of 1,000 mg. on alternate days but individual requirements differ. The onset of action is usually within 2 hours and duration is usually 6-8 hours, but may be prolonged. There were no side-effects.

In 2 patients the serum-potassium concentration was below 3 mEq./l. on the 4th and the 22nd day of therapy and the serum-CO_2 concentration rose.

The possible place of this agent in the management of a case of sporadic periodic paralysis was reported. This was a 17-year-old European male who had had periodic attacks of paralysis 2-3 times a week since the age of 6 years. The administration of 1,000 mg. of chlorothiazide after 42 days on a low-sodium diet (26 mEq. per day) resulted in the loss of 276 mEq. of sodium. During the period prior to chlorothiazide he had had 9 overt attacks of paralysis. In the 11 days after administration no attacks were recognized. The sodium intake was then increased to 226 mEq. per day and within the first 3 days 2 attacks of great severity occurred. Chlorothiazide during the period of high sodium intake did not abolish the attacks. Contrary to the findings during the first low-sodium period, during a second period of sodium restriction chlorothiazide had not prevented the recurrence of attacks, although they appeared to be of a lesser grade of severity.

The use of chlorothiazide in the management of hypertension was discussed.

We wish to express our thanks to Prof. G. C. Linder for advice and help; to the consultant staff for access to their patients; to the Misses J. Sutherland, J. Seward and M. Fischdick and Mr. R. Thomson; to Mrs. A. Ward and the die kitchen staff; and to the Medical Superintendent of Groote Schuur Hospital for facilities. We also wish to thank Messrs. Merck, Sharp and Dohme for generous supplies of chlorothiazide. Financial assistance from the U.C.T. Staff Research Fund is acknowledged.

ASSOCIATION NEWS : VERENIGINGSNUUS

UNCONTROLLED USE OF BLOOD FOR TRANSFUSION

The Cape Western Branch Council draws the attention of members of the Branch to the following letter dated 11 November 1957, which was received from the Director of Hospital Services of the Cape Provincial Administration and referred to the Branch by the Secretary of the Medical Association of South Africa:

'1. During the recently held conference of full-time superintendents of provincial hospitals, the subject of blood transfusion was discussed and the statement was made that the consumption of blood was higher per hospital in this country than elsewhere, that there were insufficient donors to supply the demand, and that it was essential to exercise the strictest control over the use of blood and reduce wastage to the minimum.

After discussion, the conference resolved as follows:

"This conference of medical superintendents of hospitals in the Cape Province has noted with alarm the wastage of blood obtained for transfusion purposes from blood-transfusion services in provincial hospitals in the Cape Province and desires to call the attention of the Medical Association of South Africa to this fact.

" The conference desires to emphasize that this wastage, if continued, must inevitably lead to shortage which will act to the detriment of patients urgently requiring blood and incidentally will endanger the cooperative relationships which at present exist between the blood transfusion services and the medical profession.

"The conference also desires to point out that the administration of blood is a potentially dangerous and an expensive form of treatment which should be only carried out under efficient and knowledgeable medical control, and considers that this control is in many instances lacking.

"The conference seeks the cooperation of the Medical Association to make known these views to its members."

'I would like to associate myself with the above views and support the request made by the Conference that your Association seek the cooperation of its members in controlling the use of blood and reducing wastage.'

IN MEMORIAM

HAYMAN ISAAC MAISTER, F.R.C.S.

Mr. A. J. Helfet, of Cape Town, writes as follows: Dr. H. I. Maister, F.R.C.S., died suddenly in Port Elizabeth on 3 January 1958. He was educated at Murchiston Preparatory School and Pietermaritzburg College. He qualified in 1927 at London, where he was a student at Guy's Hospital, and a few years later was admitted to the Fellowship of the Royal College of Surgeons of Edinburgh. His orthopaedic apprenticeship was served in Birmingham, where he was registrar and chief assistant to the late Mr. Naughton-Dunn, who was a close friend and colleague of Sir Robert Jones, and for some years Maister held appointments at the Royal Orthopaedic Hospital, Birmingham.

Dr. Maister

During the War he was one of the first to take charge of a military orthopaedic centre in Great Britain and later was posted to India, where he was promoted Lieutenant-Colonel in Charge of surgical divisions of hospitals there and in Burma.

Since his return to South Africa 10 years ago he has been senior orthopaedic surgeon to the Provincial and Livingstone Hospitals in Port Elizabeth and to the Provincial Hospital in Uitenhage. He initiated orthopaedic services in Port Elizabeth, and has represented the Eastern Cape in the National Council for the Care of Cripples, and in the South African Orthopaedic Association. He has been president of the Cape Midlands Branch of the Medical Association of South Africa. He was elected a Fellow of the British Orthopaedic Association; and—interesting as giving an indication of his leisure activities—he was first holder of the Robert Jones golf cup.

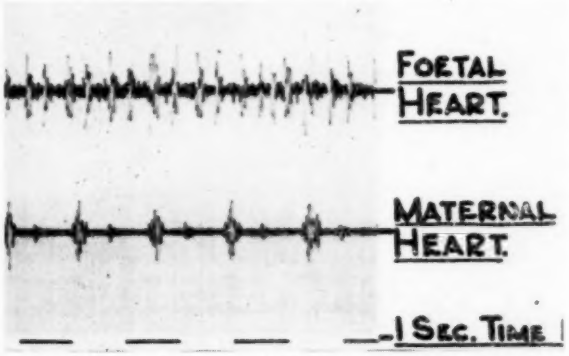
'Haine' Maister always gave unstintingly of his energy and time to all good causes, whether medical or other. He was one of these idealists who did much and spoke little of what he did, but his friends knew that his help would be immediate and unquestioning. The 'golden calf' had no place in his imagination and his hospital patients were his first responsibility. His integrity was coupled with gentleness, with kindness and with consideration. We have lost a friend of great worth, and South Africa has lost one of its ablest and most experienced orthopaedic surgeons.

All who knew him share the sorrow of his wife and two children.

NEW PREPARATIONS AND APPLIANCES : NUWE PREPARATE EN TOESTELLE

RECORDING SONISCOPE

Airsonic Ltd., who provide the following information, announce that a circuit has been designed which allows their Soniscope to be coupled to a suitable grapher so as to provide a cardiogram of the foetal heart, thus filling a definite requirement in obstetrics. The accompanying recording was taken from the outputs of 2



Record from primipara aged 32 years, 40 weeks' pregnancy in early labour.

Soniscopes—one registering the sounds of the foetal heart and the other the maternal heart. The salient features of this graph are the clear indication of the first and second beats of the foetal heart plus definite traces of patent ductus arteriosus.

The Soniscope thus continues to prove its usefulness beyond that of a frequency-discriminating, amplifying stethoscope with exceptionally high gain in the acoustic range.

Used as a stethoscope, the incorporation of high- and low-frequency attenuators allow the operator to select required groups of frequencies in the sonic range with little interference from unwanted noises. The instrument consists of a miniature, battery-operated amplifier, contact microphone and conventional headset.

The microphone has been designed to convey sounds arising from the source with which it is in contact and is insensitive to outside noises; in general, the only outside noises that are audible are those which resonate in the chest or that part of the body with which the microphone is in contact.

The amplifier is compact, measuring $4\frac{3}{4} \times 3 \times 1\frac{1}{2}$ inches, and weighs only 25 oz. It is easily carried suspended from the neck, and can be used wherever an ordinary stethoscope can be used. There are 2 output sockets, enabling 2 people to listen at the same time.

Simple to operate, the instrument has only 3 controls, one of which regulates volume and the other two discriminate against the upper and lower frequency ranges respectively. Heart sounds can be heard to the exclusion of breath sounds, and *vice versa*, and it is possible to tune out the pump noises of a cabinet respirator (iron lung) and listen only to the chest of a patient. Murmurs related to arteriosclerotic narrowing of the great vessels are readily amplified.

For use in universities and hospitals for instructional purposes, a special adaptor is available which enables 7 people to listen to the output of the Soniscope at the same time.

Sole manufacturers and world distributors are Airsonic Limited, 14 Old Queen Street, London, S.W. 1, England.

* * *

Parke, Davis Laboratories (Pty.) Ltd., have introduced Camoform, a new amoebicide for the treatment of both intestinal and extra-intestinal amoebiasis, and Dicortol (prednisolone, Parke-Davis) for the treatment of many disorders including allergic dermatoses, rheumatic fever, rheumatoid arthritis, and other connective-tissue diseases. They supply the following information:

CAMOFORM

Description

Camoform (biallylamicol hydrochloride) belongs to the a-Aminocresol family and is related structurally to the anti-malarial Camoquin (amodiaquin, Parke-Davis). Unlike many other amoebicides in common use Camoform does not contain either iodine or arsenic in its molecule. Camoform is a potent amoebicide, which has been found to be highly effective against both the intestinal and extra-intestinal forms of *Entamoeba histo-*

lytica. Laboratory studies have show Camoform to have marked action against pathogenic amoebae in dogs and hamsters as well as in man. It is relatively non-toxic and, *in vitro*, has an amoebicidal action in dilutions as high as 1 : 5,000. 70-80% of an oral dose of Camoform is absorbed in the intestines, and excretion, which is accomplished by the bile, is a slow process. Consequently blood levels fall gradually with as much as 15% of the original dose remaining in the blood for as long as 3 weeks after administration has ceased.

There is a high degree of localization of Camoform in the tissues, especially in the liver and lungs. This explains the effectiveness of Camoform not only in intestinal amoebiasis, but also in the extra-intestinal type as well. Camoform has been demonstrated to protect animals from amoebic hepatitis, even after amoebae were injected directly into the liver. A significant aspect of its chemotherapeutic action is the complete prevention of pulmonary amoebic lesions in treated animals.

That Camoform is therapeutically effective and safe in treating both intestinal and extra-intestinal amoebiasis in humans is testified to by the good results reported by many clinicians.

Indications

The treatment of both the intra- and extra-intestinal forms of amoebiasis.

Dosage and Administration

Adults, 1 to 2 tablets three times daily with meals; children (up to 12 years) ½ tablet three times daily with meals. Patients should take Camoform during meals, since taking the medication before or after meals may lead to gastric intolerance. A single course of therapy lasts 5 days (15 doses). Patients not cured with a single course should have a 3-week rest period before re-starting treatment.

Camoform is supplied in 250 mg. compressed tablets, vials of 20.

DICORTOL

Dicortol (prednisolone, Parke-Davis) is an analogue of hydrocortisone, which exhibits 3-5 times the corticosteroid activity of hydrocortisone.

Indications

The treatment of numerous conditions including allergic dermatoses, rheumatic fever, rheumatoid arthritis and other collagen diseases, inflammatory eye diseases, nephrosis and selected blood disorders.

Dosage and Administration

Dicortol is administered orally in a dosage approximately one-fifth to one-third that of hydrocortisone. Daily dosage ranges between 15 mg. and 30 mg. for several days dependent upon response and patient. The initial dosage should then be reduced by decrements of 2·5 mg. to 5 mg. at intervals of two or three days until a minimal daily maintenance dosage is achieved. Dicortol should ideally be given in divided doses after meals and before bedtime.

It is recommended that termination of therapy with Dicortol should be gradual to forestall possible rebound hypoglycaemic states resulting from abrupt withdrawal. Marked return of symptoms or concurrent stress may require a temporary increase in dosage which should then be gradually decreased to maintenance levels.

Precautions and Contra-indications

Dicortol should be administered under close medical supervision and in accordance with precautions associated with corticosteroid therapy. It should be noted that in Dicortol therapy such warning signs of overdosage as oedema, weight increase and 'moon-face' are not likely to be present. Because of possible diabetogenic effects, patients with diabetes may require higher insulin dosage while receiving Dicortol. Dicortol is contra-indicated in patients with active tuberculosis, dendritic corneal ulcer due to herpes simplex, severe hypertension, osteoporosis, psychotic states, active peptic ulcer, gastro-intestinal bleeding and thrombocytopenic purpura. The tendency to produce gastric irritation and peptic ulcer has been controlled by appropriate antacid therapy.

Dicortol is supplied in 2·5 mg. and 5 mg. scored tablets, in bottles of 30 and 100.

* * *

CHLOTRIDE (ALSO KNOWN IN THE UNITED STATES AS 'DIURIL')

Chlotride Chlorothiazide (6-chloro-7-sulphamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide) is an exceptionally potent, orally effective non-mercurial diuretic agent. It represents a new approach to diuretic therapy. Since the principal action of Chlotride is a marked enhancement of the excretion of sodium, chloride and water, it has been designated a saluretic agent. This new compound achieves a profound electrolyte and water diuresis without the attendant toxic effects and other disadvantages peculiar to the mercurials and certain other diuretic agents.

Owing to its saluretic pattern of effect and maximal oral potency and efficacy, Chlotride is ideally applicable both in initiating diuresis and in maintaining the oedema-free state in patients with congestive failure and other oedema-producing conditions and is often effective in patients refractory to mercurial and other diuretic agents. The action of this diuretic compound is unique for a number of reasons:

1. Chlotride when properly administered causes practically no disturbance of the electrolyte balance of the body because (*a*) it has a high order of activity with respect to sodium and chloride excretion, and

(*b*) the excretion of bicarbonate is minimal. Wide experience with the use of Chlotride has demonstrated that metabolic acidosis as a complication of diuretic therapy with this compound is most unlikely.

(*c*) Potassium is excreted to a much smaller extent than sodium and chloride. Potassium excretion is also relatively less than with classic carbonic anhydrase and usually does not occur when Chlotride is administered properly.

2. It is an orally effective, non-mercurial diuretic agent. It is the most potent and consistently effective oral diuretic presently available.

3. It may be characterized as a broad-spectrum diuretic, based on its enhancing effect on sodium excretion at various dosage levels. In lower doses its effect is comparable to that of the classic carbonic anhydrase inhibitors, at mid-dose levels to that of an oral mercurial, and at higher doses to that of a parenteral mercury compound.

4. Chlotride is well tolerated. It has a high therapeutic index and low inherent toxicity. Gastro-intestinal symptoms such as nausea, vomiting, and diarrhoea are reportedly rare even at maximal therapeutic dosage levels.

5. This saluretic agent can be administered even in the presence of severe cardiac, renal or hepatic disease.

6. Onset of action following oral administration is rapid (within 2 hours) and the duration of effect moderate (6-12 hours).

7. The diuretic effectiveness of Chlotride does not decrease with repeated daily administration in single or multiple doses. This continued effectiveness operates until fluid and electrolyte retention has been corrected. The early refractoriness characteristic of the classic carbonic anhydrase inhibitors does not occur.

Dosage. Detailed literature on request. Chlotride is supplied in 0·5 g. tablets in bottles of 25 and 100.

Manufacturer, Merck Sharp & Dohme International Division of Merck & Co., Inc. Enquiries, P.O. Box 5933, Johannesburg.

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S.A. PHARMACEUTICAL JOURNAL AND DR. M. SHAPIRO

The firm of solicitors acting for the *South African Pharmaceutical Journal* has been directed to write to the *South African Medical Journal* as follows:

'An article published in the *S.A. Pharmaceutical Journal*, of December 1957, wrongly ascribed to Dr. M. Shapiro a certain report delivered to the last Medical Congress in Durban. Because of the error, certain erroneous impressions have been created and our clients have hastened to withdraw the article concerned and apologise to Dr. Shapiro in terms of Annexure 'A' hereto attached, which will appear in the February edition of our clients' journal.

'We have been informed that the article complained of has gained wide currency in the medical profession and, as this may cause unnecessary embarrassment to Dr. Shapiro, an esteemed member of your profession, we have taken the liberty of sending you Annexure 'A' for favour of publication in the news column of your esteemed publication.'

Annexure 'A': Apology and Retraction

In the December 1957 issue of . . . (*the S.A. Pharmaceutical Journal*) . . . , under the heading 'Not Only Caesar's Mother', we wrongly ascribed to Dr. Maurice Shapiro a report delivered to the last medical congress in Durban, and we expressed certain views thereon.

We referred to Dr. Shapiro (*a*) as reporting that about four times as many paying patients as free patients in the Transvaal are delivered of their babies by the Caesarean route, and as speculating whether that had to do with their ability to pay for 'a pretty expensive bit of surgery'; (*b*) as criticizing certain of his colleagues as 'surgical know-alls' capable of almost anything; (*c*) as quoting examples of doctors who use 'blunderbuss massive treatment with expensive antibiotics' and of patients put on a cortisone life without much justification; and (*d*) as blandly contending that 'people of minimum training undertake work which is little short of malpractice'.

Our commentary then added: 'And Dr. Shapiro's the man who at the same conference ditched the Pharmaceutical Society's efforts to talk to doctors about reserving for the pharmacist, free of economic competition from the medical profession, the work of dispensing for which he trains five long years. A doctor gets no more than a few hours training at dispensing. . . . One might speculate who indeed in this case, are the people of minimum training!'

We have now learned that, apart from being present at the inauguration ceremony on the first night, Dr. Shapiro did not attend the last medical congress at all, that he made no such report then or at any other time, and that in fact he strongly disapproves of the terms of that report.

Our whole commentary was therefore entirely misconceived and completely unjustified. We have tendered to Dr. Shapiro our sincerest apologies, and we hasten to publish at this, the earliest opportunity, this expression of our profound regret and unconditional withdrawal of our commentary and of the remarks made therein. In particular we apologise for the unjust imputation that Dr. Shapiro was critical and derogatory of his colleagues, and for our unjust reference to him as having 'ditched' the Pharmaceutical Society's efforts. We also wish to record that there was no intention at all to reflect on Dr. Shapiro's integrity and propriety and on his high standing in the profession.

PASSING EVENTS : IN DIE VERBYGAAN

Mr. L. W. van Blerck, F.R.C.S. (Edin.) who has previously been on the full-time orthopaedic staff of the Johannesburg General Hospital, has taken over the orthopaedic practice of the late Mr. H. I. Maister, F.R.C.S. (Edin.) of Port Elizabeth. His address is 4 Rose Street, Port Elizabeth. Telephones: Rooms 2-5757, if no reply 2-1545.

* * *

First International Congress of Endocrinology. The International Executive Committee (chairman, Dr. Christian Hamburger, Statens Seruminstitut, Copenhagen) have issued a preliminary notice concerning this Congress, which is to be held in Copenhagen, Denmark, in July 1960 under the presidency of Prof. Bernardo A. Houssay of Argentina. The subjects to be dealt with are to be chosen by an international Programme Sub-Committee (chairman, Dr. G. Pincus, Shrewsbury, Mass., USA); they will be of general interest to endocrinologists, and will include chemical, biological and clinical aspects. The official languages will be English, French, German and Spanish. The Congress will be open to all who may be interested. Further information may be obtained from the Congress Secretary, Dr. Svend G. Johnsen, Statens Seruminstitut, Copenhagen 5, Denmark. Later announcements will follow.

REVIEWS OF BOOKS : BOEKRESENSIES

TUBERKULOSE VAN DIE VROULIKE GESLAGSORGANE

Tuberculose Der Vrouwelijke Geslachtsorganen. Proefschrift. Door Iwan Désiré Johanns. Pp. 209. 14 Figure. Assen: Van Gorcum & Comp. N.V. 1957.

Inhoud: Inleiding. I. Voorkomen en localisatie. II. De pathogenese. III. De pathologische anatomie. IV. De diagnostiek: 1. De klinische diagnose. 2. De bacteriologische diagnose. 3. De histologische diagnose. 4. De röntgenologische diagnose (Hysterosalpingografie). 5. De pertubatie. 6. De diagnose door laparotomie, laparoscopie en culdoscopie. 7. De diagnose door curettage, microcurettage en zuigcurettage. 8. De diagnose door punctie van adnextumoren. 9. De diagnose door onderzoek van cervixsecreet en vaginaalslijm. 10. De diagnose door onderzoek van het menstruatiebloed. V. De symptomatologie. VI. De terapie. 1. de conservatieve behandling. 2. de operatieve behandling. VII. De prognose. VIII. Het klinisch materiaal. IX. Het na-onderzoek en de resultaten der behandeling. X. Casuïstiek. XI. Samenvatting. Summary. Literatuurlijst.

Hierdie boek bestaan uit 'n proefskrif ter verkryging van die graad van dokter in die geneeskunde aan die Ryks-universiteit te Groningen, Nederland.

Genitale tuberkulose by die vrou word op uitvoerige wyse bespreek en die resultate wat verkry is by die behandeling van hierdie kwaal aan die Groningense Universeit-Vroeukliniek word nagegaan. Daar word ook deeglik op die betrokke literatuur ingegaan. Ter afsluiting verskyn daar 'n samevatting in beide Nederlands en Engels.

Dit is te betwyfel of hierdie proefskrif enige oorspronklike bydrae tot die vraagstuk van genitale tuberkulose by die vrou bevat.

E.M.S.

CEREBRAL LIPIDOSES

Cerebral Lipidoses. A Symposium. L. Van Bogaert, M.D., Chairman; J. N. Cumings, M.D., F.R.C.P., Editor; A. Lowenthal, M.D., Associate Editor. Pp. x + 212. Figs. 42s. Oxford: Blackwell Scientific Publications. 1957.

Contents: Preface. List of Participants. Introduction, by L. van Bogaert. The histological classification of diffuse demyelinating cerebral sclerosis, by W. Blackwood. Histochemical study of primary lipidoses by P. D. Diezel. Cephalinlipidosis, by H. S. Baar. Spastic amaurotic axonal idiocy, by Th. Rabinowicz and E. Wildi. Histochemistry and the study of lipidosis and allied diseases by G. W. F. Edgar. Histochemical investigations of degenerative diffuse sclerosis (leucodystrophy and diffuse sclerosis of the Krabbe type), by P. B. Diezel. A histochemical study of the pre-lipid and metrachromatic degenerative products in leucodystrophy, by Th. v. Hirsch and J. Peiffer. The position of gargoylism amongst the spingolipidoses on the basis of the histochemistry of cellular storage substances, by F. Seitelberger. Histochemistry and classification of the Pelizaeus-Merzbacher disease. The chemistry of copper phthalocyanin staining for phospholipids and its application to the lipidoses. Discussion (G. W. F. Edgar, H. G. Sammons, J. N. Cumings, A. G. Everson Pearse). Identification and quantitative determination of the lipids of the nervous system, by A. Froehlich. The diagnostic value of lipid estimations in the cerebral lipidoses, by J. N. Cumings. Determination of gangliosides in nervous tissue, by L. Svennerholm. The nature of the gangliosides in Tay-Sachs' disease, by L. Svennerholm. Chemical analysis and histochemical examination of an atypical case of Tay-Sachs' disease, by P. Favarger and E. Wildi. The nature of the lipids in the brain in Niemann-Pick's disease, by G. Bartsch. Chemical pathology in gargolyism, by G. Brante. Leuco-dystrophy as an 'inborn metabolic error', comparable to lipidosis, by G. W. F. Edgar. A new method for the isolation of cerebron from brain tissue, by C. Chatagnon. The composition of the acetalphosphatides of the brain. Index.

This Symposium (as its contents clearly show) is of greater interest to the neurohistologist and biochemist than to the clinician; in fact the discussion chiefly centres around problems of technique. It can therefore only be summarily reviewed in a clinical medical journal.

The discussion is not confined to what clinicians usually understand by the term lipi(o)doses, i.e. the amaurotic idiocies, xanthomatosis, Gaucher's disease, Niemann-Pick's disease, Pelizaeus-Merzbacher's disease and Gargoylism.

The first contribution to the symposium is by W. Blackwood on the histological classification of diffuse demyelinating cerebral sclerosis. This shows the trend of this neuro-chemical and neurohistological discussion. Clinicians do not link up the demyelinating diseases (disseminated sclerosis, Devic's neuromyelitis optica, acute disseminated encephalomyelitis, etc.) with the lipiodoses but to the neurochemist, who is interested in the type of lipid which replaces the myelin, this link is natural. In fact it seems quite possible that greater knowledge of neurochemistry may in future necessitate a revision of our present classification of the lipiodoses and the leucodystrophies.

In the meantime one would advise the reader who wishes to get clinical information about the lipiodoses to read the chapter in question in such textbooks as Brain's 'Diseases of the Nervous System' or Schaltenbrands 'Die Nervenkrankteiten' and use the symposium only if he wants more detailed information on the histology or the chemistry of any of the above-mentioned lipidoses.

F.H.K

EPIDEMIOLOGY

Uses of Epidemiology. By J. N. Morris, M.A., F.R.C.P., D.P.H. Pp. viii + 135. 17s. 6d. net plus Postage 9d. abroad. Edinburgh and London: E. & S. Livingstone Ltd. 1957.

Contents: Introduction. I. Historical Study. II. Community Diagnosis. III. Working of Health Services. IV. Individual Chances. V. Completing the Clinical Picture. VI. Identification of Syndromes. VII. In Search of Causes. Recapitulation; General. Appendix. References—General. Index to Subjects.

This thought-provoking, stimulating and provocative little publication, which, as the author states, can in no way be considered comprehensive, serves to indicate by practical examples how the epidemiological approach to many of the non-communicable diseases can be applied. It has in the main been written for the practising clinician and should in addition serve as a means of bridging the divide between the curative and the preventive fields of medicine.

By the application of epidemiological methods the question as to whether a particular feature or entity is a problem or not can be answered, provided that the collected and collated data is accurate in so far as the group or condition under scrutiny is concerned.

I have no hesitation in recommending this most readable, well-printed, just-over-a-hundred-page little book to all students of clinical and preventive medicine. Close study of examples of these newer epidemiological avenues of investigation which it opens up will, without any doubt, be handsomely repaid.

E.D.C.

GERIATRICS

Modern Trends in Geriatrics. Edited by William Hobson, B.Sc., M.D., D.P.H. Pp. vii + 422. Figures 68. 81s. 6d. plus 1s. 10d. delivery. London: Butterworth & Co. (Publishers) Ltd. South African Office: Butterworth & Co. (Africa) Ltd., P.O. Box 792, Durban. 1956.

Contents: Introduction. 1. General Problems of Aging. 2. Aging from a Biological and Cellular Point of View. 3. Normal Values and the Interpretation of Biochemical Data in the Elderly. 4. Psychological Aspects of Aging. 5. Arteriosclerosis and Hypertension. 6. Glycosuria and its Significance. 7. Chronic Bronchitis in the Elderly. 8. Skin Conditions in the Elderly. 9. Gynaecology in Senescence and Senility. 10. Orthopaedic Surgery in the Elderly. 11. Anaesthesia for the Elderly. 12. Therapeutics in the Elderly. 13. Nutritional Problems of the Elderly. 14. Physical Medicine in the Treatment of the Elderly. 15. Hospital Care of the Elderly. 16. Problems in the Home. Care of the Elderly. 17. Employment, Retirement and Health. Index.

This volume constitutes a timely and successful effort by a team of renowned experts steeped in learning, experience and highly qualified to extract the best from the spate of recent literature on geriatrics, resulting from the intensification of world problems by the unprecedented increase in the numbers of old people.

But even the most accomplished work cannot avoid imperfections, some admittedly inevitable. The rapid advance of medicine and the unavoidable interval between writing and publishing a book prevents the authors keeping pace with advances. Hence some recent developments failed to find a place in the book.

There are flaws due to over-cautiousness, contributors being shy to venture a little off the well-trodden path—an attitude laudable in text-book compilers, but not in recorders of 'trends'. The justified warning against prolonged courses of antibiotics should have been supplemented by an estimate of the value of vitamins and antifungal medicaments as antagonists to the risks involved.

The ganglionic blocking drug Pentholinium is enthusiastically recommended for hypertension. Highly effective though it frequently is, it nevertheless remains unsuitable for office and general practice, even in the rare patient able to weigh his symptoms objectively.

Some statements display the dogmatism appropriate to an undergraduate teacher. Most scientists agree that aging has more than one cause just as many reject the writer's opinion that the various causes are *not* interdependent or interrelated. The assertion 'Physical vigour is closely dependent on mental vigour' will be strongly supported by those holding the view that '*Mens sana in corpore sano*' applies even to oldsters.

However, it has to be admitted that all the shortcomings are mostly of a negligible nature; therefore no criticism can detract from the high merits of this multidimensional symposium. Its authors have produced a thoughtfully prepared, concisely written, authentic appraisal of modern trends in geriatrics.

As it contains a wealth of very instructive information and advice it is bound to be of inestimable value to doctors and to others interested in promoting the welfare of the aged.

I.M.H.

THE RETICULO-ENDOTHELIAL SYSTEM

Physiopathology of the Reticulo-Endothelial System. A Symposium organized by The Council for International Organizations of Medical Sciences. Established under the joint auspices of Unesco and W.H.O. Edited under the direction of B. N. Halpern by B. Benacerraf and J. F. Delafresnaye, C.I.O.M.S. Pp. xii + 317. Illustrations. 45s. Oxford: Blackwell Scientific Publications. 1957.

Contents: Foreword. Introduction. The Morphology and Physiology of the Reticulo-Histiocytic Cell. The Principles of the Determination of the Shape and Dimensions of Globular Proteins in Solutions. Physiologic Stimulation and Inhibition of the Phagocytic Function of the Reticulo-Endothelial System. Physiology of Phagocytosis of Particles by the R.E.S. Factors Controlling Phagocytosis. Physico-Chemical Factors governing the Phagocytic Function of the R.E.S. Hepatic Reticulo-Endothelial Cells as Participants in the Normal Disposition of Exogenous Cholesterol in the Rat. The Role of the Reticulo-Endothelial System in Haematoclasia. The Role of the Reticulo-Endothelial System in Iron Metabolism. Local Defences against Infection and their Relation to the General Reticulo-Endothelial Defences. Phagocytic Activity of the Reticulo-Endothelial System in Experimental Infections. The Role of the Reticulo-Endothelial System in the Reaction to Endotoxins. The Effect of Cortisone on the Synthesis and Distribution of Antibodies in Rabbits sensitized with Iodine 131 Labelled Human Albumin. On the Nature of some Tissue Hypersensitivity Reactions. Factors Influencing Production of Cirrhosis and Ascites in Dogs following Massive Irradiation of the Reticulo-Endothelial System with Radioactive Gold Colloids. Changes of the Storage Capacity of the R.E.S. during Different Pathological and Pharmacological Conditions. The Reticulo-Endothelial Cells in Health and Disease. Summing-up.

The usefulness of this book lies in the fact that in it are collated a series of papers, by well-known workers, on the functional activity of the reticulo-endothelial system. The functions particularly stressed are phagocytic activity, metabolic functions, and role of the R.E.S. in the defence against bacterial infection. The results of the experiments and the techniques used provide valuable information in themselves, but in addition the discussion on each paper by a panel of experts adds greatly to the value of the book.

The majority of articles will be of interest only to the research worker and are restricted to certain aspects of a not-so-limited subject. However, there are a few articles written on a review basis including recent advances, that can be assimilated and profitably read by the average medical man no matter what his sphere of interest or practice. In this connection those dealing with the role of (*a*) the R.E. system in haematoclasia, (*b*) the nature of some tissue hypersensitivity reactions and (*c*) the reticulo-endothelial cells in health and disease, can be especially singled out.

Except for a few obvious errors of spelling that can be eliminated and an odd article which contributes little to existing knowledge on this subject, the general standard of this work is high.

C.J.U.

ANAESTHESIA AND OTOLARYNGOLOGY

Anaesthesia and Otolaryngology. By Donald F. Proctor, M.D. Pp. xv + 267. Figs. 33. 87·00 Baltimore: The Williams & Wilkins Co. 1957.

Contents: Preface. *Section I. General Considerations.* 1. Mortality and Morbidity Associated with Otolaryngological Surgical Procedures. 2. Pre-operative Preparation of the Patient. 3. Pre-anaesthetic Medication and Ancillary Drugs. 4. Pulmonary Ventilation during Anaesthesia. 5. Postanesthetic Care. 6. Medicolegal Considerations. *Section II. Otolaryngological Procedures under General Anesthesia.* 7. Tonsillectomy and Adenoidectomy. 8. Operations on the Paranasal Sinuses. 9. Surgery of the Ear. 10. Operations on the Larynx or Trachea. 11. Peroral Endoscopy and Bronchography. *Section III. Otolaryngological Procedures under Local Anesthesia.* 12. General Considerations Regarding Local Anesthetics. 13. Tonsillectomy. 14. Surgery of the Nose, Nasal Septum, Ethmoid and Sphenoid Sinuses. 15. Miscellaneous Minor Procedures. 16. Peroral Endoscopy and Bronchography. *Section IV. Other Aspects of Problems Common to Anesthesiology and Otolaryngology.* 17. Respiratory Resuscitation. 18. High Airway Obstruction and its Relief. 19. Ventilation Problems in the Unconscious Patient. 20. Intrathoracic Disease. 21. Respiration Resuscitation in the Newborn. Index.

While the need for maximum co-operation between surgeon and anaesthetist is universally stressed, the lack of a full understanding of each others problems is, all too often, a barrier to the realisation of ideal team work. An author, therefore, who can speak as an expert in both fields, is in a position to make a most valuable contribution. Dr. Proctor has made good use of his opportunities in producing something quite different from the ordinary text-book on surgical or anaesthetic subjects.

The earlier chapters are devoted to general principles aimed at the reduction of operative mortality and morbidity, and the safe handling of the patient before, during and after operation. The author then describes his own techniques, both general and regional, for anaesthesia in a number of common procedures in otolaryngology, using them with good effect to illustrate matters of principle. The closing section of the book deals with a number of specialized topics of interest to both surgeon and anaesthetist.

While Dr. Proctor's work is fully up to date, he displays a refreshing conservatism throughout, and a truly physiological approach to all problems. Whether or not the reader agrees with him in all details, it is obvious that his views are based on wide experience and that the interests of the patient are invariably his first care. Descriptions are characterized by a wealth of practical detail which is not found in many works of this kind.

The book is simply written and is not overburdened with technicalities. It will be read with interest, pleasure and profit by surgeon and anaesthetist alike.

J.C.N.

YEAR BOOK OF DERMATOLOGY

Year Book of Dermatology and Syphilology. By Dr. Rudolf L. Baer, M.D. and Victor H. Witten, M.D. Pp. 464. Figs 62. 87·00. Chicago: The Year Book Publishers Inc. 1957.

Contents: Publisher's Note. Introduction. Allergic Eczematous Contact Dermatitis. 1. Treatment and Prevention. A. Endocrine Therapy. B. Physical Therapy. C. Other Therapy. 2. Eczematous Dermatitis, Atopic Dermatitis and Urticaria; Allergy. 3. Drug Eruptions. 4. Miscellaneous Dermatoses. 5. Cancers: Precanceroses; Other Tumors. 6. Fungous Infections. 7. Other Infections; Infestations. 8. Venereal Diseases and Their Treatment (Exclusive of Gonorrhoea). 9. Investigative Studies. 10. Miscellaneous Topics.

This ever-popular work again makes its appearance under the able direction of Rudolf Baer and Victor Witten. The former's well-known work on Cross-sensitization fits well into the leading article, entitled 'Allergic eczematous contact dermatitis'. This also contains references to modern work on immunology, on the problem of antibodies in humans and animals with eczematous contact allergy, on non-specific factors of importance such as acid and alkali-neutralization and much else of interest. A bibliography of over 60 references loses much of its value for the busy practitioner (for whom this book is intended) by having no corresponding numbers in the text.

The abstracts are of their usual high standard and are selected from many parts of the world; as is natural, a large proportion (188) derive from the U.S.A., 50 from other English-speaking countries, 48 from Germany, 28 from Scandinavia, 20 from France and 47 from all other countries. As in previous editions this serves to present the North American reader with abstracts of at least some of the work being done in the rest of the world. 'English-speaking' reminds one that the excellent example in style formerly set by Dr. Sulzberger is, on the whole, still being followed; a few examples of 'jungle English', such as 'contacted' for 'touched' and 'solubilize' where 'dissolve' expresses the meaning more accurately, are creeping in and should be guarded against.

The use of anti-malarial drugs in various conditions is rightly given several pages, but the tranquillizers are obviously losing ground.

The antibiotics, including Mycostatin, are considered, as are numerous recent advances in therapy with trypsin, hyaluronidase, selenium sulfide, plasma cholinesterase and other substances.

New clinical and laboratory findings regarding pathogenic fungi are given 18 pages and should be read by all bacteriologists who are faced with routine mycological specimens.

Over 100 pages are devoted to investigative studies and are a model of précis-writing; from the remainder of the book no important work has been omitted; it can be confidently recommended to physicians who wish to keep in touch with the progress of dermatology and will, as usual, be acquired by all dermatologists.

L.J.A.L.

MEDICAL TREATMENT

Medical Treatment. By Kenneth MacLean, M.A., M.D., F.R.C.P. Pp. vii + 696. 50s. net. London: J. & A. Churchill Ltd. 1957.

Contents: Preface. 1. Diseases of the Heart. 2. Hypertension and Diseases of the Blood-vessels. 3. Diseases of the Blood. 4. Diseases of the Upper Respiratory Passages and Ears. 5. Diseases of the Bronchi, Lungs and Pleurae (excluding Tuberculosis). 6. Tuberculosis. 7. Disease of the Alimentary Tract. 8. Diseases of the Liver, Gall-bladder and Pancreas. 9. Diseases of the Spleen and Lymph Glands. 10. Renal Diseases. 11. Diseases of the Nervous System. 12. Diseases of the Meninges and Cerebro-spinal Fluid. 13. Epilepsy, Syncope and Vertigo. 14. Mental Illness in General Practice. 15. Diseases of Connective Tissues, Muscles and Joints. 16. Diseases of the Skeleton. 17. Diseases of the Skin. 18. Diseases of the Endocrine Glands. 19. Diseases of Metabolism. 20. Diseases due to Bacterial Infections. 21. Infections due to Viruses and Miscellaneous Agents. 22. Tropical Diseases. 23. Diseases due to Worms and Flukes. 24. Venereal Diseases. 25. Acute Poisoning. 26. Fluid and Electrolyte Disturbances. 27. A.C.T.H. Cortisone and Allied Steroids. 28. Antibiotics and the Sulphonamides. Index.

The last twenty-five years has been a golden era in medical treatment and today it is becoming increasingly difficult to keep abreast of the bewildering array of therapeutic agents now available. In spite of this, many standard text-books are concerned more with aetiology and diagnosis and little stress is laid on treatment. Dr. McLean's comprehensive volume dealing with this aspect of medical practice fills a real need. He covers the therapy of individual diseases in considerable detail, being concerned not only with specific agents but also with various symptomatic and nursing measures for the patient's comfort. In conditions where several alternative forms of therapy are available he makes his own preferences quite clear and ends up by mapping out a suggested regime of treatment. In an age of tablets it is quite refreshing to find the inclusion of an occasional prescription which he has found helpful. The chapter on tuberculosis is especially well done and he rightly stresses the hazards of drug resistance and the benefits of B.C.G. vaccine. In addition, two separate sections are included on the uses of steroids and antibiotics which should prove helpful to those, like your reviewer, who are confused by the great number of different proprietary agents which are available. Another helpful point is the inclusion of both the apothecary and the metric dosage of most drugs in common use.

Although there are no major criticisms to be made of the general layout of this book, there are several minor points with which issue can be taken. For instance, on the basis of recent studies, there seems no justification for the recommendation of hydrochloric acid as an adjuvant to oral iron therapy. It is also somewhat surprising to find the complex metabolic derangement of salicylate intoxication dismissed as a 'severe acidosis'. In addition, the section on electrolyte therapy is so short as to be of limited value to anyone faced with an individual patient and the inclusion of formulae for the calculation of deficits hardly seems warranted. One thing which would certainly be helpful in the next edition is a fuller bibliography so that the sources of some of the statements can be studied in more detail.

This book can be recommended to a wide public. It should not only assist the physician and general practitioner but should also supply a balanced therapeutic approach for the senior medical student. Occasional inaccuracies are more than balanced by the advantages of a single authorship where repetition is avoided and the author's own stamp is always apparent. The book is well produced and is moderately priced.

T.H.B.

CORRESPONDENCE : BRIEWERUBRIEK

WITHHOLDING OF WATER BY URBAN BANTU MOTHERS

In an industrial practice which includes a fair proportion of work in Windermere, Cape, I find that cooperation by Bantu mothers in the treatment of gastro-enteritis and allied conditions in babies, is not as full as one would like it to be. One sometimes visits a pondok to see a marasmic baby. On the table there is a bulging-full paper bag of dried skim-milk supplied by the local hospital the week previously; or, perhaps, two or three half-full bags supplied over several weeks and a partly-used bottle of Darrow's solution concentrate.

In particular I find that the mothers fail to carry out advice about administration of fluids, whether instructed by the interpreter at the doctor's surgery or given a printed sheet of directions at the hospital out-patient department. In cases referred to hospital for parenteral salines, how often does it occur in the experience of the G.P. or intern that no more is heard until some days later when the husband or some other male offshoot calls for a death certificate!

Rumour-talk in Windermere has it that babies with gastro-enteritis are not always given sufficient fluids. Some women believe that water should not be given to sick babies because it will invite the water-snake to bite them. This is an ancient legend perpetuated by the witch-doctors.

Six colleagues in industrial practice were asked whether they knew of this curious and dolorous belief; none had heard of it but two suggested that it might be due to fear of bilharzia infection. Asked whether they thought that Darrow's concentrate should be coloured with a dye to make it more acceptable as 'medicine', only one colleague agreed; and he said that Europeans as well as Natives expected medicine to be coloured.

A female Bantu interpreter with 18 months' nursing experience in the Coronation Hospital, Johannesburg, was instructed to make a survey in Windermere. In this survey women of child-bearing age were asked, 'Do you think that water should be given to sick babies? Is it good or bad for them'? The 136 Bantu subjects were divided into 63 'backward' and 73 not 'backward'. They are classified in the following table according to the opinions they expressed:

	Water is		
	Good	*Bad*	*No Opinion*
Not backward	29	26	18
Backward	0	34	29
Total	29	60	47

Even in such a small survey, the figures are disquieting.

No method is suggested of converting the water-deniers into water-givers. The solution probably lies between long-term prospects of general education and instruction in hygiene by Bantu social workers (not to mention improved housing and wages), and open and immediate competition with the cool-drink vendors by the issue of electrolytes in coloured tablets with added dashes of effervescent and saccharin.

I have noticed a decline in breast-feeding among the Bantu, and this even in tribal-type women and apart from cases where mothers are absent at work. Is this because urbanization is altering their customs relating to family-spacing? Or is it due to the impact of 20-feet high advertisements for tinned infant foods with large pictures of fat bouncing babies? Early weaning seems in some cases to be related to sorcery—evil spells, occult poisons, alleged physical effects of jealousies, and the like.

These would seem to be subjects for investigation by social scientists.

I wish to thank Dr. I. Mirvish for bringing certain items to my notice.

L. Ruskin

20 Salt River Road
Salt River, Cape
25 January 1958